



AUGUST 1956

# BULLETIN

OF THE NEW YORK  
ACADEMY OF MEDICINE





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ACADEMY OF MEDICINE

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THE TREATMENT OF HEMOLYTIC STREPTOCOCCUS INFECTIONS AND THE NEWER APPLICATIONS OF SULPHANILAMIDE\*

REUBEN OTTENBERG

THE HEMOLYTIC streptococcus ranks among the prime causes of disease. Perhaps second to the pneumococcus as a direct cause of death, it probably is more frequently responsible for acute infections than any other germ. This is particularly true if one includes not only the diseases directly due to it, such as scarlet fever, tonsillitis, erysipelas, suppuration, puerperal fever, but the possible indirect effects attributed to it, such as glomerulonephritis and the recrudescences of rheumatic fever. It is responsible for at least one fifth of all cases of septicemia<sup>1</sup>.

Within recent years there has been great progress in knowledge of the biology of the hemolytic streptococcus, and in the past two years, with the advent of a remarkable and highly effective chemotherapy there has been renewed activity in the study of these infections with perhaps an unfortunate tendency to think that sulphanilamide has closed the chapter. This is far from being the case. And it is important not to lose sight of the valuable advances of recent years in the biology and immunology of the streptococcus. For this reason I will discuss this subject first.

\* Delivered April 15, 1938 in the Friday Afternoon Lecture Series.

## CLASSIFICATION OF STREPTOCOCCI

The hemolytic streptococci form a large group of closely related organisms.<sup>2</sup> They are of great viability, remaining alive in air and dust for long periods of time and from five to thirty per cent of adults are carriers. The importance of the hemolytic property as a unifying biological characteristic began to be stressed at the turn of the century when blood cultures came into use for diagnosis. Brown, in his monograph of 1919,<sup>3</sup> used the hemolytic character as a chief differential point, classifying streptococci into alpha or viridans, beta or hemolytic, and gamma or non-hemolytic. In blood plates the clear rings of hemolysis around the colonies are characteristic. The red cells undergo complete clearing.

A great number of the earlier attempts at subdivision of the hemolytic streptococci failed because the cultural and biological characters of the sub-groups did not correspond to clinical divisions and so many separate strains were found that no grouping was possible.

In recent years, however, many of these difficulties have been circumvented by new immunological studies. Two important new classifications have been introduced, based on different principles, not mutually exclusive but supplementing each other.

The first of these, introduced by Lancefield<sup>4</sup> and her co-workers, is based on a simple precipitin reaction, as antigen is used a carbohydrate (often called substance C) extracted from the bacteria themselves with hot hydrochloric acid, as antibody, the serum of rabbits immunized with formalized bacteria. With this method hemolytic streptococci from all sources are found to fall readily into seven sharp groups.

Cutting across and supplementing this classification is typing by the method of agglutination. Unsatisfactory attempts to type hemolytic streptococci have been made for years. But recently by a slight simplification of technic Griffith<sup>5</sup> has shown that hemolytic streptococci derived from human sources can be classified by agglutination with immunized rabbit's sera into twenty-eight (or perhaps more) fixed types analogous in many ways with the fixed types of pneumococci. These strains maintain their specificity for years, certain of them have special pathological or epidemiological peculiarities.<sup>6</sup> Four of the types (Nos. 7, 16, 20 and 21) have now been eliminated<sup>7</sup> as not belonging to Lancefield's group A. The others are all pathogenic for man and are found with varying incidence in all kinds of hemolytic streptococcus.

affections It is of the greatest importance that one and the same strain may be responsible for entirely different clinical diseases<sup>8</sup> Already grouping (A to G) and typing of strains (within Group A) are helping to clear up many epidemiological problems

Before going into the hotly debated and still not entirely settled question of the specificity of certain streptococci it is necessary to say a few words about the five known toxins of the hemolytic streptococcus

TABLE I  
CLASSIFICATION OF STREPTOCOCCI

BROWN 1919 <i>Culture on Blood</i>	LANCIEFIELD 1933 <i>Specific Precipitation</i>	GRIFFITH 1935 <i>Specific Agglutination</i>
Alpha ( $\alpha$ ) Viridans		
	A—Pathogenic, of human origin—but causing mastitis in cows by contact with human carriers—hence milk borne epidemics of sore throat and scarlet fever	Twenty-four or more permanent types, numbered between 1 and 28
Beta ( $\beta$ ) (Hemolytic)	B—Chiefly bovine C—In various animals }	Four or more types known (Nos 7, 16, 20, 21)
	Cause disease in animals—may be harbored in human throat, vagina or intestines, but as a rule without causing disease	
	D } E } I usually saprophytic F } found chiefly in foods G }	
Gamma ( $\gamma$ ) (Non-Hemolytic)		

## TOXINS

The hemolysin (often called streptolysin) is the toxin which has been known longest It is liberated in culture media and can be assayed quantitatively It is not limited in its action to human red blood cells but acts on the cells of many different animals An antibody to it (anti-streptolysin) frequently occurs in human disease particularly of course in hemolytic streptococcus diseases and has recently become of clinical importance<sup>9</sup> Antibodies to streptolysin have been difficult to produce in animals but recently Todd<sup>10</sup> has shown that streptococci from human infections (Group A) have two lysins, one of these is a true toxin whose

injection leads to the production of neutralizing antibodies in animals it is labile in the presence of oxygen. The other, like the hemolysins produced by the non-human streptococci of groups B, C, D and E, is oxygen stable and non-antigenic.

The second known toxin of hemolytic streptococci, a leukocidin, has been little studied because of difficulties of technique. It probably plays an important rôle in killing not only leukocytes but also other cells and hence probably in the local (pyogenic) effects of hemolytic streptococci.

A third toxin (if it deserves the name) is a ferment-like substance, fibrinolysin,<sup>11</sup> capable of dissolving fibrin. It is specific for human fibrin and is formed only by Group A streptococci. There is no evidence that it plays a rôle in the spread of streptococci through the tissues unless it does so by influencing the character of the exudate.

Until recently a soluble toxin fatal to animals had not been demonstrated in culture filtrates. But in 1934 Weld<sup>12</sup> succeeded in extracting such a toxin of great potency from the surface of young organisms. This lethal principle always accompanies hemolysin but is not identical with it.

The fifth and most important (from the practical view) is the erythrogenic toxin. The study of this has played a large rôle in the question of the specificity of certain strains of streptococci. While the existence of an erythrogenic toxin was presumed after the discovery of the Schultz-Charlton reaction in 1918 (blanching of the scarlet fever eruption locally on intracutaneous injection of convalescent scarlet fever serum), proof of the definite existence of a soluble exotoxin capable of producing erythema only when injected into the skin of susceptible humans was the result of the work of G. F. and Gladys Dick.<sup>13</sup> It is often spoken of as the "Dick Toxin." It has had the most widespread application in the prevention and treatment of scarlet fever, an application which I cannot discuss here.

The great question of the specificity of the scarlet or erysipelas toxins is still in dispute<sup>14</sup> with the best of authorities and arguments on each side. Since the experts cannot agree it would seem best for the outsider to accept some intermediate view, such as that put forward by Hooker<sup>15</sup> and by Gay,<sup>16</sup> all hemolytic streptococci produce more or less erythrogenic toxin, each toxin being a mixture containing different quantities of different toxin moieties. An antitoxin formed against a strain of broad polyvalency and high toxin production (such as most

strains from scarlet fever) may neutralize erythrogenic toxin from many other sources

Such a view is capable of explaining many otherwise irreconcilable observations such as the immunity of some individuals to certain scarlet fever toxins but not to others,<sup>17</sup> the failure of commercial antitoxin to neutralize the toxin of some scarlet fever strains, the occurrence of scarlet fever in Dick negative persons, the permanence of immunity to scarlet fever and the impermanence of immunity to erysipelas, the undoubted efficacy of scarlet antitoxin and scarlet convalescent serum in some cases of erysipelas and other streptococcus infections, and so forth

### SERUM TREATMENT

The multiplicity of hemolytic streptococcus strains probably forms only a partial explanation for the failure of most polyvalent antistreptococcus sera in human infections in the past. It is not very difficult to produce in horses sera which will influence streptococcus bacteremia in laboratory animals if the bacteremia is due to strains similar to those used for immunization. Such sera are usually phagocytosis-promoting rather than bactericidal or antitoxic. Even if the promotion of phagocytosis should turn out to be of great importance, the experience of recent years with type specific antipneumococcus sera shows how unlikely it is that any polyvalent antibacterial serum as yet produced can have enough antibody to be of more than occasional and accidental efficacy for organisms of such widely different serological strains as the streptococci.

What place has serum treatment then (since the introduction of sulphanilamide) in the treatment of hemolytic streptococcus infections other than scarlet fever? In actual practice ordinary polyvalent antistreptococcus serum has too little value to be further considered. In erysipelas the specific antitoxin<sup>18</sup> (and equally scarlet antitoxin) has considerable therapeutic effect although probably less than has sulphanilamide. The trend of recent clinical opinion is that scarlet fever convalescent serum is superior (despite lower antibody content) to the animal derived antitoxin,<sup>19</sup> not only in scarlet fever but in all sorts of other hemolytic streptococcus infections.<sup>20</sup> Such convalescent sera are not available everywhere but most of our large cities now have serum centers where convalescent sera are carefully gathered.<sup>21</sup> New York is fortunate in having such a center under charge of William Thalheimer

Some may think the advent of sulphanilamide has made sera superfluous but this is not so. There are cases in which sulphanilamide has to be stopped because of idiosyncrasies. There are cases in which it is ineffective. There is also evidence that the drug and serum supplement each other: the serum is antitoxic and the drug is antibacterial; certainly they do not interfere with each other. For this reason in every desperate case of hemolytic streptococcus infection it would seem wise to supplement the drug with the serum—by preference convalescent scarlet fever serum when available.

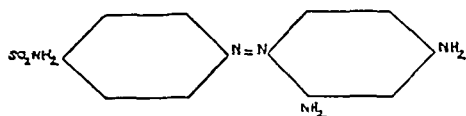
### CHEMOTHERAPY

When I was asked over a year ago to give the present lecture the request was that I should discuss the then new chemotherapy for streptococcus infections. At that time the status of the new drugs was less certain than it is now and I hesitated to commit myself to present the subject a year later. For this reason I chose the non-committal title "Treatment of Hemolytic Streptococcus Infections".

However, within the past year I have had an opportunity to follow over a hundred treated cases myself, and the literature has presented an enormous amount of new information. It is perfectly clear now that for the first time a successful bacterial chemotherapy has been found. And it promises to have a far wider usefulness than originally appeared probable. In fact it is one of the major advances of our generation.

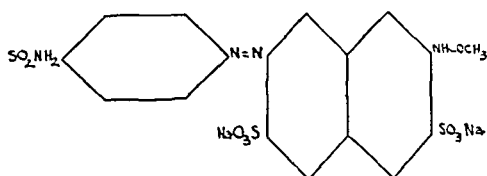
The curious round about course of progress in this field is interesting.<sup>22</sup> Before 1935 there had been innumerable attempts to find a chemical which would have a specific effect on various kinds of bacteria. None of these had been successful. In the majority a start had been made with some substance known to have bacterial killing properties in the test tube. Heidelberger and Jacobs<sup>23</sup> had pointed out that there was a certain chemotherapeutic effect from molecules containing the azo coupling, for example para-amino-benzene-sulphonamide-azo-hydrocupreine. Whether it was this or pure chance that led Domagk in 1935<sup>24</sup> to try the effect of the dye, prontosil (though it had no bactericidal effect in the test tube) is not known. At any rate his experiments on the hemolytic streptococcus sepsis of mice and rabbits were clear cut and conclusive and were immediately confirmed by Levaditi and Vaisman,<sup>25</sup> and at once led to effective use of this dye by oral administration in the treatment of streptococcus infections.<sup>26</sup>

## CHART I



THE ORIGINAL PRONTOSIL  
(Prontosil rubrum Prontosil flavum  
Sulphonamide-chrysoidin)

A red crystalline substance no longer  
in use



PRONTOSIL SOLUBLE

Now generally called PRONTOSIL

A red solid usually supplied in 2½%  
solution (formerly known also as  
Streptozon)



SULPHANILAMIDE

(Prontylin, etc)

Para-amino-benzene-sulphonamide

The original dye, prontosil, is a very insoluble substance and has the property of staining the entire body intensely. A related dye, of a much more complex structure but very much more soluble and convenient, known as prontosil soluble or prontosil solution soon replaced it. This could be given by intramuscular or, if necessary, even by the intravenous route. It had the same peculiar properties, having no effect on bacteria in the test tube but nevertheless curing experimental and clinical infections.

Within a few months a further simplification was introduced by Tréfouel<sup>27</sup> and associates. They found that para-amino-benzene-sulphonamide was the common factor not only in prontosil but in a large series of other more or less active compounds. With this drug, which has now been given the name of sulphanilamide, they obtained both in mice and rabbits results quite as good as those obtained with prontosil. Their work was quickly confirmed<sup>28</sup>.

Sulphanilamide represents about one half of the molecule of the more complex drugs, and the azo linkage which was originally thought to be essential to the therapeutic effect is not present. Sulphanilamide (intro-

duced under the trade name, prontosil), unlike prontosil, is not a new drug covered by patents, but is a long-known chemical compound which any competent chemist can make. It is now produced by a great many different pharmaceutical houses under different names. The Council on Pharmacy of the American Medical Association has recommended<sup>29</sup> that the name sulphani­lamide be used, while a shorter name might perhaps be desirable it seems best to adhere to this name. The term prontosil when used now refers to soluble prontosil.

Fuller<sup>30</sup> in England and Marshall<sup>31</sup> and associates in the United States have cleared up some of the mystery about the effect of prontosil, both of the original forms of prontosil liberate sulphani­lamide in the body and it is possible that their therapeutic effect is due entirely to the sulphani­lamide liberated. Soluble prontosil liberates about one-third of its weight of sulphani­lamide.

#### SULPHANILAMIDE

Sulphani­lamide is a colorless solid, somewhat soluble in water (0.8 per cent) but most conveniently given by mouth in the solid form. Its easy solubility in fat may turn out to have considerable significance.<sup>32</sup> The study of its mode of action and practical use have led to certain very important observations. In the presence of a very limited number of bacteria and a suitable environment the drug is slightly bactericidal. It is, however, unmistakably bacteriostatic, that is to say, provided the number of bacteria is not too great, it definitely slows down the rate of growth of hemolytic streptococci. It was claimed by Levaditi<sup>33</sup> at the very beginning that its major effect was not only on the bacteria but on the specific hemolysin and leukocidin (and by inference the other toxins of the streptococci). This has received confirmation in a recent remarkable piece of research by Osgood and Brownlee<sup>34</sup> in which the effect of the drug was observed on infected cultures of human bone marrow. When dissolved in broth or in salt water the drug has little killing effect on streptococci. When dissolved in the serum of such animals as the mouse or the guinea pig, which have slight natural resistance to streptococci, the drug has a distinct inhibitory effect on growth but is unable to accomplish sterilization. When dissolved in serum such as that of man and monkey which in itself has considerable bactericidal power for streptococci, the drug greatly enhances this bactericidal power so that numbers of organisms such as may occur in human infections, namely

up to 500 per cubic centimeter, are completely killed

According to earlier work of Buttle, Colebrook and associates<sup>35</sup> in England and Long and Bliss<sup>36</sup> in this country, fairly high concentrations (1/10,000 or 10 mg per 100 cc) in serum are necessary to accomplish sterilization, and dosage has accordingly been adjusted to bring about such a concentration. But if the recent work of Osgood and Brownlee<sup>34</sup> is correct the drug is effective at a much higher dilution in human serum, only 1/100,000 (or 1 mg per 100 cc of serum). If this turns out to be true (and its confirmation will require further clinical as well as experimental studies) we shall require much smaller doses than we have been using.

It is probable from all the recent work that the drug does not work in the body only by direct killing of bacteria but also by neutralizing the aggressive poisons of the bacteria. Colebrook<sup>37</sup> at first thought that the effect depended on stimulation of phagocytosis. But the drug is bactericidal in the test tube when added to human blood from which practically all of the leukocytes had been filtered (method of Flemming). Mellon and his group have shown that even when it appears to cure infection the drug does not kill all the bacteria in the tissues. This explains the observation made almost at the beginning of the work by Levaditi<sup>38</sup> that in mice which had apparently recovered, recurrence of the infection and death might occur at any time from one to thirty days after administration of the drug had been stopped. Similar clinical observations have been made in man. For this reason the appropriate procedure is to continue treatment for at least four or five days after the apparent cessation of infection. Fortunately in man these recrudescences are much less frequent and serious than in mice because man has a very much higher immunity to hemolytic streptococci.

#### ABSORPTION AND EXCRETION

Within the past year careful work on absorption and excretion of the drug by Fuller<sup>39</sup> and by Marshall<sup>31</sup> have taught us much concerning the best method of administration. Absorption of sulphanilamide from the gastrointestinal tract is very rapid. In ordinary dosage most of the drug administered is absorbed in four hours. If it be possible to use the gastrointestinal tract there is no advantage in parenteral administration. By repeated administration at intervals of three or four hours the concentration of sulphanilamide in the blood can be steadily raised to five, ten,

fifteen or even more milligrams per 100 cc of serum Long and his associates<sup>36</sup> believe the blood level should be kept at ten milligrams per 100 cc but many others<sup>40</sup> have obtained excellent results with lower concentrations (4-7 mg per 100 cc) Marshall<sup>31</sup> has shown that in patients with large daily divided doses it takes three days for the blood level to reach an equilibrium and a blood concentration of ten to fifteen milligrams per 100 cc can be maintained easily It takes about three days after the drug is discontinued for the blood to free itself if such a level has been reached

Marshall has devised a simple clinical method of determining the concentration of the drug in the blood Such determinations ought to be made occasionally in most cases and frequently in critical cases Long and Bliss<sup>36</sup> pointed out on clinical grounds and Osgood<sup>34</sup> and others have shown on experimental grounds that continuous treatment is essential The drug must not be omitted during the night The continuous presence of low concentration in the blood is more important than intermittent high concentration The drug penetrates well into tissue fluids, into pleural exudates, cerebrospinal fluid and hence into all the tissues but in none of these places does it reach as high a concentration as in the blood For this reason it is frequently advisable to inject 0.8 per cent sulphanilamide (made from the pure crystalline product) in normal sodium chloride solution into the spinal fluid in meningitis and into the pleura in empyema cases<sup>41</sup> In patients to whom the drug for any reason can not be administered by mouth, one has a choice between intramuscular administration of the dye solution prontosil, or the subcutaneous infusion of 0.8 per cent sulphanilamide The question of the relative effectiveness of these two procedures is not yet settled Certainly prontosil administration leads to a much lower concentration of sulphanilamide in the blood than does the administration of sulphanilamide directly, but it seems nevertheless to be clinically about as effective Both drugs are rapidly absorbed when given intramuscularly or subcutaneously and it is probably never advisable to give either drug intravenously

Both soluble prontosil and sulphanilamide are excreted rapidly in the urine, the latter is certainly excreted in the bile This has led to valuable applications of these drugs particularly in the treatment of infections of the genito-urinary and biliary tracts In treatment of urinary infections the concentration of the drug in the urine is important Marshall<sup>42</sup> has shown that in man and the rabbit a part of the drug is excreted in

conjugation as a para-acetyl derivative while in dogs it is all excreted in its original form, that is as sulphanilamide. The important thing is probably the concentration of unaltered sulphanilamide which is easily determined by Marshall's method. With renal impairment of course the excretion of the drug is slower and the effect to be expected in urinary infections is not so great, hence the administration of the drug must be more cautious and must be checked by more frequent blood examinations on account of the possibility of its accumulating in the blood.

### DOSAGE

It is quite possible that on the basis of Osgood and Brownlee's<sup>34</sup> recent work a smaller dosage than at present used will be found satisfactory. But for the present at least it will be best to adhere to the dosage worked out by Colebrook<sup>35</sup> and by Long<sup>36</sup> on essentially clinical grounds. It is important to attain the desirable concentration in the blood as rapidly as possible, for this reason a large amount of the drug should be given during the first twenty-four hours. The usual dosage of sulphanilamide is figured at approximately one gram for each twenty pounds of body weight in twenty-four hours with an average upper limit for adults of five or six grams. But during the first day of treatment in any serious case and during many days of treatment in very desperately serious cases, considerably larger doses up to a total of ten or even fifteen grams per day have been given with success.<sup>43</sup>

The danger of toxic effects or idiosyncrasy seems to be no more with large than with ordinary doses. After the first few days, if the symptoms are abating and there is no bacteriemia, the dosage may be reduced. Half dosage is continued for four or five days after the infection has apparently subsided.

When prontosil is used the dosage for twenty-four hours can be calculated most conveniently as one cubic centimeter of the 2½ per cent solution (obtained in ampoules on the market) for each pound of body weight except that for persons over one hundred and fifty pounds in weight it is better to reckon on three quarters of a cubic centimeter per pound. As in the case of sulphanilamide the daily dosage should be divided and given at from four to six hour intervals. When prontosil and sulphanilamide are given together a gram of sulphanilamide can be taken as approximately equivalent to twenty cubic centimeters of prontosil.

## CHART II

AVERAGE DOSAGE OF PRONTOSIL OR SULPHANILAMIDE  
FOR SEVERE INFECTIONS

In twenty-four hours, *For every twenty pounds body weight up to 120 pounds,*

SULPHANILAMIDE 1 gram (15 grains) by mouth or subcutaneously,  
or interchangeably,

PRONTOSIL 20 cc intramuscularly

Dose should be distributed as uniformly as possible throughout the twenty-four hours, e.g., for an average adult 1 gram sulphani-*lamide* (or 20 cc prontosil) every four hours *day and night*

For the first twenty-four hours in particularly dangerous infections 50 per cent or 100 per cent more may be given

After temperature is normal half dosage is continued for five to fourteen days according to severity of the case

## TOXIC EFFECTS

The drug on the whole is remarkably non-toxic. In animals it is necessary to give almost incredibly large doses<sup>44</sup> to produce toxic effects or death. In human beings any toxic effect other than minor inconveniences is extremely rare.

The cyanosis which occurs with the use of the drug can hardly be regarded as a toxic effect. It occurs in over 60 per cent of all patients and is not accompanied by dyspnea or diminished oxygen carrying capacity of the blood.<sup>45</sup> Sulphemoglobinemia or methemoglobinemia was at first thought to be the cause of the cyanosis<sup>46</sup> but now is believed to be extremely rare.<sup>47</sup> It has been thought that the sulphemoglobinemia was due to administration of sulphates,<sup>46</sup> generally in the form of magnesium sulphate. The real cause of the cyanosis is unknown, it may be some black oxidation product of the drug on the surface of the red cells.<sup>45</sup> In general it is important to remember that cyanosis is to be expected, unless other symptoms appear it is not to be regarded as a reason for discontinuing the drug.

Certain subjective symptoms frequently occur. These are nausea, vomiting, headache, slight dizziness and mental confusion. In rare cases these symptoms are enough to prevent administration of the drug. I have the impression that they occur chiefly in nervous individuals who expect them or realize that they are getting an unusual form of treatment. They are almost never the precursors of more serious toxic symptoms and can as a rule be disregarded. They are just as likely to occur after very small doses as after large doses.

A common but not serious effect is a mild degree of acidosis<sup>48</sup> This can usually be relieved by mere administration of bicarbonate of soda and in fact it is wise to give bicarbonate of soda, one gram for each gram of the drug administered as a routine in all cases

Both in animals and in man long continued administration of the drug does not produce any delayed toxicity or late secondary effects When the drug has been given a considerable number of days and the patient's temperature has come to normal, there is occasionally a secondary rise of temperature without further symptoms of infection This "secondary fever" is probably due directly to the drug itself and the temperature returns to normal when the drug is stopped<sup>49</sup> I have seen this phenomenon a number of times It is very puzzling and the decision to stop the drug calls for a nice clinical discrimination

All the other described toxic effects of the drug must be classified as idiosyncrasies, that is, as abnormal results which cannot be produced in the vast majority of cases even by very large doses The possibility of these idiosyncrasies is important to keep in mind although they are very rare indeed, when they occur some of them are very serious

Anemia is commonly regarded as the most important idiosyncrasy Severe degrees of anemia are so common in almost all the infections for which the drug is used that it is often questionable whether an anemia which occurs is really due to the drug However, there have been a considerable number of cases of acute hemolytic anemia reported<sup>50</sup> Jaundice or hemoglobinuria may accompany the anemia I have seen only one such severe case with hemoglobinuria These cases have almost all recovered when the drug was stopped and one or two blood transfusions given but there probably have been some deaths Anemia of the aplastic type has been described It is extremely rare but is much more dangerous than the hemolytic anemia Agranulocytosis must be extremely rare also, but there have been several cases attributed to the drug<sup>51</sup> In animal experiments and clinical observations the drug seems to have only a very slight if any depressing effect on the leukocyte count or the bone marrow Anemia can develop in two or three days and it is important in all cases under treatment to repeat blood counts frequently One case of a transient optic neuritis<sup>52</sup> has been ascribed to the drug and one case of apparent generalized allergy (urticaria, sneezing and dyspnea)<sup>53</sup> There have been a considerable number of cases of a peculiar widespread dermatitis<sup>53 54</sup> Rather definitely the drug sensitizes the skin to light and

dermatitis has occurred chiefly in ambulant patients who exposed themselves to direct sunlight. The discovery of porphyrin<sup>55</sup> (a hemoglobin degradation product capable of sensitizing to light) in the urine of these cases may explain this and perhaps other idiosyncrasies. The eruption is morbiliform, does not affect the mucous membranes, is often accompanied by fever up to 103° and usually does not persist longer than about three days even if the drug be continued. Persons who have once had the eruption are likely to get it again if the drug be resumed.<sup>56</sup> Some of the patients have developed it after a single small dose. Schwenkter<sup>53</sup> saw it in ten of 180 patients, a large proportion of them ambulant. We have seen three cases in approximately 150 hospitalized patients. On account of the rare idiosyncrasies sulphanilamide in spite of its vast usefulness must be considered a dangerous drug. Most of the accidents have occurred after small doses which shows how great a rôle special susceptibility plays. It is important that druggists should not supply this drug to the public for self medication. All patients receiving it should be under daily medical supervision, especially for the first few days of administration.

### CHART III

#### PRECAUTIONS TO BE TAKEN DURING TREATMENT WITH SULPHANILAMIDE AND PRONTOSIL

- 1 Patient must be examined in a good daylight at least once a day, (for jaundice, anemia, eruptions)
- 2 Urine must be watched daily for hemoglobin or bile
- 3 Blood count must be made every day for first three days then every two days
- 4 Bicarbonate of soda must be given (in a dose about equivalent to sulphanilamide) to prevent acidosis

### PUERPERAL INFECTIONS

The earliest practical application of sulphanilamide was in the treatment of puerperal hemolytic streptococcus infections. Colebrook and his co-workers, who made the first comprehensive report in 1936,<sup>57</sup> have recently reviewed one hundred cases<sup>58</sup> and show a striking reduction in mortality, from 22.8 per cent for 495 cases in the preceding five years, to 8 per cent in the last one hundred cases. Their series included fifteen patients with positive blood cultures and six with general peritonitis, and one half or more of both these groups recovered. Not only were the recoveries greater in number but the secondary develop-

ment of parametritis (almost the rule in puerperal sepsis cases before this) was very rare, 5 per cent. It is interesting that not all the streptococci were killed off, as 48 per cent of the cases still showed them in vaginal smears at the time of discharge from the hospital. Their work has been confirmed by other workers<sup>59</sup> and there is no doubt that sulphanilamide represents an immensely valuable remedy in puerperal infections. It is possible that routine use of small doses after childbirth, especially in cases exposed to infection, might greatly reduce the incidence of puerperal infections since the experimental work all indicates that the drug is far more effective against incipient than well developed infections.

### MENINGITIS

There is no field in which the effects of sulphanilamide therapy have been so dramatic and conclusive as in the treatment of streptococcus meningitis. The mortality before the advent of this drug was 95 per cent to 97 per cent according to the statistics of Neal<sup>60</sup> and of Gray<sup>61</sup>. The first recovery with prontosil treatment was reported by Causse in February 1936 and this was followed by reports by Schwenkter, Vitenson, Neal and others<sup>62</sup>. Neal and Applebaum<sup>63</sup> reported the largest series of cases personally observed—of seventeen cases in which there was no question of the diagnosis thirteen recovered. Bliss and Long<sup>64</sup> reported recovery in twenty-four out of twenty-eight cases of hemolytic streptococcus meningitis with which they had had contact. This confirms the experience of other reports in the literature and indicates a recovery of something like 75 per cent of the cases.

In the treatment of streptococcus meningitis the administration of the drug must be prompt and vigorous and it is advisable (although not all authors agree that it is necessary) to give the drug intraspinally as well as by mouth or intramuscular injection. In the intraspinal administration it is important to use only the 0.8 per cent solution in saline made up with pure crystalline sulphanilamide (which can be obtained from Winthrop or from Du Pont). Prontosil has been tried intraspinally but Schwenkter<sup>62</sup> warns against it as it seems to be irritating and less effective than sulphanilamide. The intraspinal treatment is carried out by replacing about ten to twenty cubic centimeters of spinal fluid with sulphanilamide about twice in twenty-four hours until the spinal fluid becomes cleared of streptococci on smear and culture. Oral or intra-

muscular treatment is continued for a considerable period longer, for ten to fourteen days, or until the patient is entirely well, but for the latter part of the period the dosage can be reduced to one-half or one-third. It is important that the surgical indications should be met despite the advent of the new drug. If a suppurating focus such as mastoiditis or sinusitis requires surgical drainage, this should be carried out. It is very likely that prophylactic administration of sulphanilamide in cases in which meningitis is to be feared, such as mastoiditis or brain injuries, may reduce the incidence of this form of meningitis.

#### STREPTOCOCCUS INFECTIONS OF OTHER SEROUS MEMBRANES

In streptococcus infections of the eye, the peritoneum, the pleura, joints and other serous surfaces, sulphanilamide has yielded extraordinarily good results. I have seen two cases of streptococcus peritonitis which recovered promptly with the drug. Three out of four cases of streptococcus pleurisy in the stage in which there was not yet frank pus have recovered under sulphanilamide therapy.<sup>65</sup> As streptococcus pleurisy most commonly occurs as a complication of streptococcus bronchial pneumonia, the sputum in every case of bronchial pneumonia ought to be more carefully studied for the presence of *Streptococcus hemolyticus* than it has been in the past. It would seem indicated to treat streptococcus bronchial pneumonia such as so commonly follows measles and influenza with sulphanilamide both because it is a streptococcus infection of the lungs and for the prevention of the frequently occurring empyema.<sup>66</sup> It is no longer therefore enough to get a laboratory report that there are or are not pneumococci present in the sputum but the presence of hemolytic streptococci should also be determined and acted on.

#### ERYSIPELAS

From the very beginning the reports of treatment of erysipelas with the new drug have been very striking and it might safely be said that although there are occasional cases that do not respond to it, its use is the optimal method of treating the disease. Peters and Havard<sup>66</sup> reported on forty-seven cases in every one of which the spread of the disease was arrested in twenty-four hours and in forty-three of which the temperature was normal in forty-eight hours. The duration of the disease is regularly shortened by the drug.<sup>67</sup> One of the most important

uses is in the erysipelas of very young infants<sup>65</sup> in whom there is usually bacteriemia and a very high mortality (94 per cent) On account of the synergistic action of specific serum and sulphanilamide reported in other connections it would seem wise in severe cases of erysipelas to use both the antitoxic serum and the drug

### SCARLET FEVER

There is very little evidence that sulphanilamide has any effect in scarlet fever<sup>65</sup> Peters and Havard<sup>66</sup> reviewed 150 cases and were not able to find sufficient differences between the treated and untreated cases to demonstrate any effect of the drug on the toxic phase of the disease However, there was a slight difference in the development of suppurative complications, 56 per cent of the untreated and only 35 per cent of the treated patients developed such complications It is therefore possible that sulphanilamide will be of use in the more severe cases of scarlet fever as a preventive of suppurative complications If so used, of course it should be in addition to antitoxic or convalescent serum

### RHEUMATIC FEVER

In spite of the well established association of hemolytic streptococci with recrudescences of rheumatic fever, all the evidence at hand is that sulphanilamide and the allied compounds not only have no therapeutic effect on rheumatic fever itself<sup>68</sup> but also according to a recent small but very carefully studied series of cases,<sup>69</sup> have no effect in preventing recrudescences when used for the streptococcus infection Indeed the toxic effects of the drug seem to be increased in rheumatic fever In chronic arthritis likewise the drug has been disappointing<sup>70</sup>

### TONSILLITIS AND SEPTIC SORE THROAT

Every one has reported excellent results in severe cases of tonsillitis and septic sore throat as well as in suppurative sinus infections due to the hemolytic streptococcus However, on account of the possibility of untoward reactions the drug should not be used as a routine for ordinary sore throats but should be reserved for more menacing infections True, the idiosyncrasies are of very rare occurrence but if one were to produce an aplastic anemia or an agranulocytosis, even though only once out of ten thousand times, as the result of the treatment of a disease in itself

relatively harmless, one would be open to blame. On the other hand in a serious infection the chance of an idiosyncrasy is very small as compared with the danger of the disease.

### STREPTOCOCCUS SURGICAL INFECTIONS AND SEPTICEMIA

In all varieties of surgical infections due to hemolytic streptococcus, sulphanilamide is indicated and should be used vigorously. In septicemia (for example in sinus thrombosis) the drug has accomplished results such as have never been seen before. However although recoveries have been reported with sulphanilamide and without operation,<sup>71</sup> it does not yet seem so certain that the drug will cure any given case that one is justified in omitting surgical removal of the infected focus (e.g., the infected thrombus in the lateral sinus).

### THE USE OF SULPHANILAMIDE IN INFECTIONS OTHER THAN BY HEMOLYTIC STREPTOCOCCUS

Sulphanilamide was originally introduced as a specific for hemolytic streptococcus infections. Further laboratory and clinical investigation has shown it to have a much wider field of usefulness.

Concerning other forms of streptococci than the typical hemolytic streptococcus (beta) of Lancefield's group A, occasional infections do occur with organisms from animal sources and it is interesting that there have been reports of successful use of the drug in cases of group B but failures in groups D and G.<sup>72</sup> There has also been a report of the effective use of the drug in guinea pigs against a streptococcus of group C which produces a natural acute disease in these animals.<sup>73</sup> The drug promises great economic usefulness in bovine mastitis.<sup>74</sup> In infection with *Streptococcus viridans* and other non-hemolytic streptococci nearly all observers have reported clinical failure although the drug in the test tube is stated by Long to have an effect on some strains of the organism. Neal reported having seen one recovery in *Streptococcus viridans* meningitis among three cases of meningitis due to non-hemolytic streptococci for which the drug was tried. In subacute bacterial endocarditis the results have been uniformly unfavorable.

Sulphanilamide has so far had little trial for anaerobic infections. It protects mice against intraperitoneal inoculation with *Clostridium welchii*<sup>75</sup> and I have seen one striking recovery in postabortal septicemia due to the anaerobic *Streptococcus foetidus* of Viellon (later described

by Schottmuller as *Streptococcus putridus*) Good results have also been reported in gas gangrene <sup>75</sup>

With *Staphylococcus aureus* infections there have been almost no reports of definite favorable therapeutic effects Our own attempts with the drug in *staphylococcus* septicemia were all ineffective

### PNEUMOCOCCUS

In pneumococcus infections Sanford Rosenthal<sup>77</sup> and others have shown sulphanilamide is well worth using It has a distinct effect on the highly virulent type III<sup>78</sup> as well as some effect on type I<sup>79</sup> and other types <sup>80</sup> It has a greater effect in animals than in man In pneumococcus meningitis Neal<sup>63</sup> reports three recoveries among twenty clinical cases This is not a large proportion but as these were the only recoveries seen in her twenty years' experience, the drug is worth trying The drug and the specific serum, experimentally at least, have an additive result <sup>79</sup> Hence, it would seem worth using the drug alone for pneumococcus infections for which no serum is obtainable, particularly the very virulent type III, and perhaps along with serum for other severe cases In the use of the drug for pneumonia there is one inconvenience, namely, the pseudocyanosis due to the drug In severe cases it is necessary to judge the degree of anoxemia by the respiratory rate and determinations of the oxygen saturation of the arterial blood rather than as usual by the appearance of the patient

### MENINGOCOCCUS

Until recently animal experimentation with meningococci was rather unsatisfactory but by the new method (C P Miller) of injecting the organisms suspended in a protecting solution of mucin a virulent form of meningococcus peritonitis can be produced in mice With this method Proom showed that the drug protects mice against otherwise overwhelming infections <sup>81</sup> With the meningococcus (as with the pneumococcus) the drug and the immune serum combined have a greater effect than the sum of the individual effect of the two agents <sup>82</sup> The use in clinical meningococcus meningitis has been so recent that there is not yet at hand a report of a large series of cases but Long reports<sup>83</sup> that Schwenkter has observed fifty-five cases treated with the drug with a mortality of 19 per cent as compared with a mortality of 30 per cent in a control group treated with serum Neal<sup>76</sup> reports eighteen meningitis cases of which

thirteen recovered While the case fatality is not strikingly reduced she has the clinical impression particularly in a few very malignant cases that the drug has an unmistakably beneficial effect Its method of administration in meningitis was discussed earlier in the present paper Recent workers however find the intraspinal administration of sulphanilamide unnecessary this simplifies the treatment greatly

### OTHER GRAM NEGATIVE ORGANISMS

Concerning the influenza bacillus, Neal<sup>63</sup> reports the work of Provitzy who found prontosil combined with immune serum to have some curative action on the otherwise fatal infection of mice with influenza bacilli Neal and Applebaum report recovery in one out of ten cases of influenza bacillus meningitis so treated

The protective effect of sulphanilamide against gram negative bacilli was first demonstrated by Buttle and co-workers<sup>64</sup> They showed that the drug in relatively small doses protects mice against one hundred to one thousand otherwise fatal doses of typhoid or paratyphoid bacilli With Friedlander bacilli experimental work by Buttle was discouraging

Helmholz<sup>65</sup> showed that sulphanilamide is active against *B. coli*, *B. capsulatus aerogenes* and the proteus bacillus He pointed out in fact that the drug is effective against practically all the common urinary infections except that with the *Streptococcus fecalis* (variety of non-hemolytic streptococcus) and it is fortunate that we have in mandelic acid a drug which has a very pronounced effect on the *Streptococcus fecalis* Sulphanilamide is peculiarly adapted to be of aid in the very common and stubborn urinary infections with bacilli of the proteus group These organisms resist many of the ordinary urinary antiseptics because of the strong alkaline reaction which they create but the effectiveness of sulphanilamide is greatly enhanced by this very alkalinity

The latest gram negative organism to succumb to sulphanilamide is the Ducrey bacillus Boris Kornblith<sup>66</sup> has reported highly favorable results in twenty-two of twenty-three cases of chancroid

The use of sulphanilamide in gonococcus infections is also a matter of relatively recent discovery Surprisingly prompt cures were shown in thirteen of nineteen cases reported by Dees and Colston<sup>67</sup> from Johns Hopkins Hospital in May 1937, and there has been wide experimentation with the drug in practically all genito-urinary clinics since then<sup>68</sup> The consensus of opinion seems to be that with oral administration of sul-

phanilamide without any other therapy a rapid cure can be expected in about half the cases. Good results have been reported in prostatitis, arthritis, ophthalmia and other complications.<sup>80</sup> A certain proportion of the cases seem to be resistant to the drug. What factors cause this uneven response is not yet known. Due to the fact that gonococcus cases are usually ambulant, while most of the other diseases for which sulphanilamide has been used are not, and that exposure to sunlight undoubtedly increases the susceptibility to skin eruptions, the majority of the cases which have shown skin idiosyncrasies have been reported from genito-urinary clinics. Gonorrhea is a disease which is generally curable by other means and it is possible that the drug will in the future be reserved for systemic, complicated or otherwise resistant cases of gonococcus infections.

### URINARY INFECTIONS

In the genito-urinary organs the drug acts not only in virtue of its already recognized effect in the tissues, but also because of its excretion, in far higher concentrations in the urine than it ever reaches in the blood. Fuller<sup>80</sup> early in 1937 showed that when prontosil is given by injections, sulphanilamide is excreted in the urine (along with prontosil). In this case sulphanilamide appears in the urine only from four to six hours after the injection of prontosil. On the other hand when sulphanilamide is given by mouth it appears as such in the urine very rapidly and in very high concentrations. Marshall and his co-workers<sup>31</sup> showed that whereas in the dog all the drug is excreted as sulphanilamide, in man as well as in the rabbit about one-half is excreted in a conjugated form as a para-acetyl derivative and this acetylated form is stated to be almost inactive. Marshall's very delicate method of quantitative testing enables one to estimate the quantity of sulphanilamide in the urine with considerable accuracy. Helmholz and his associates<sup>85</sup> and Long and his associates<sup>36</sup> found that a concentration of 75 to 200 mg per 100 cc of the free drug is needed for a satisfactory bactericidal effect in the urine. It was found by Helmholz clinically<sup>90</sup> that the drug shows distinctly increased effectiveness in alkaline solution. The administration of sodium bicarbonate should never be omitted when the drug is given as a urinary antiseptic. The total volume of urine is naturally of importance when determining the bactericidal efficiency. Long recommends that the twenty-four hour volume be kept as nearly as possible eighteen hundred

cubic centimeters by the administration of fifteen hundred cubic centimeters of milk and four hundred cubic centimeters of orange juice. The concentration which the drug reaches in the urine will depend to a considerable extent on renal function. If optimal results are to be expected it is necessary to test this concentration frequently.

Aside from bacterial infections the drug has been tried with no success in syphilis but with definite curative results in malaria.<sup>91</sup>

### INFECTIONS OF UNKNOWN NATURE

In the future undoubtedly many more uses will be found for sulphanilamide. Modifications of it or of other drugs of greater potency or specificity will probably be discovered. In its use great stress has been laid on accuracy of bacteriologic diagnosis but on account of the unexpected versatility of the drug it seems worth using at present in any very grave infection of unknown nature. For example, I have recently seen recovery in two cases of pyelophlebitis. This is a disease the bacteriology of which is seldom discovered except at the postmortem table; then the organisms found are commonly some intestinal inhabitant such as streptococci, colon bacilli or anaerobes. In desperate cases of this kind, although the bacteriology cannot be determined, the drug is well worth a trial.

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## THE MODERN TREATMENT OF DIABETES\*

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THE MODERN treatment of diabetes presupposes a knowledge on the part of the physician of the principles of treatment. These principles may be thus enumerated

PRINCIPLES OF TREATMENT

1 *Weight* Maintain the patient at or slightly below the ideal body weight

2 *Number of Feedings* Divide the day's food allowance into three meals and three supplementary feedings. This will reduce the frequency of insulin reactions. Even diabetic patients who do not require insulin do better on frequent feedings. With protamine insulin, the bedtime feeding is especially necessary.

3 *Protein Requirements* Provide one gram of protein per kilogram of body weight per twenty-four hours for adults and from two to three grams for children during their rapidly growing periods.

4 *Carbohydrate Requirements* Provide carbohydrate somewhere in the middle range 120 to 200 grams per twenty-four hours.

5 *Fat Requirements* Restrict fat to the least possible amount consistent with the maintenance of an ideal body weight. For the purpose of reducing an obese diabetic the fat should be limited to 50 or 60 grams per twenty-four hours and for normal weights should not exceed half the carbohydrate. If the patient is undernourished the fat can exceed this figure.

6 *Vitamin Requirements* The deficiency in fat soluble vitamins inherent in the low fat diets should be overcome by adding vitamin concentrates to the diet.

7 *Insulin Requirements* Give enough insulin to keep the urine sugar free without reactions. That means not more than an occasional trace of sugar.

\* Delivered March 18, 1938 in the Friday Afternoon Lecture Series.

8 *Urinalyses* Control the insulin dosage by means of four separate daily urinalyses, not by a single specimen or a twenty-four hour specimen

9 *Blood tests* Blood tests are unnecessary for the control of glycosuria, but *are* necessary to detect a developing hypoglycemia

10 *Infections* are particularly hazardous to a diabetic. Therefore avoid acute infections and eliminate sources of chronic infection

These principles constitute a guide for the treatment of diabetes. If they are constantly kept in mind as objectives, the treatment of the disease becomes simplified and will be more successful.

### EDUCATION OF THE PATIENT

The modern treatment of diabetes also presupposes the intelligent cooperation of the patient. The patient or some member of the family should know how to do three things, namely, calculate the diet, test his urine for sugar, give himself insulin.

Calculation of the carbohydrate, protein and fat content of the diet is not the burden it is commonly supposed to be. A well trained patient consumes perhaps five minutes a day at this task. A dietitian can teach a patient in one hour how to calculate his diet. Facility in making the calculations can then be acquired only by daily application to the task on the part of the patient.

For this instruction the services of a trained dietitian is advisable. If no dietitian is available, a nurse or even another diabetic patient can undertake the task. Expense to the patient is negligible compared with that necessary for nursing service in any other medical condition, for only one or two visits are required. The effort involved will be repaid many times by the increased well-being and security of the patient.

*The task of calculating the diet should definitely be removed from the shoulders of the physician.* It is no more the duty of the physician to calculate his dietary prescriptions than it is to compound his drug prescriptions. When this is fully recognized the general practitioner will approach the new diabetic patient with less perturbation, for the dietary requirements of a diabetic patient can be expressed in a single prescription of three figures. Indeed, the management of a diabetic fits particularly well into the work of a busy practitioner, because, when properly conducted, the patient does the routine work and the physician acts as consultant at semi-weekly, weekly, or monthly intervals depending

on the severity of the case

In reviewing in detail the actual management of a diabetic patient it is convenient to discuss the subject under four headings 1) Diet, 2) Insulin, 3) Complications, 4) Significance of laboratory findings

## DIET

How does one determine the dietetic requirements of a diabetic patient? The task is really very simple. The one food substance that has to be supplied in adequate amount is protein. Existence can be maintained without fat and without carbohydrate, but protein is indispensable to life or even health. *Moreover for a given weight the protein requirement is a constant, regardless of the activity of the patient.* A 145 pound farmer working hard in the field needs no more protein than a book-keeper of the same weight sitting at his desk, provided the farmer consumes enough carbohydrate and fat to supply the extra calories needed for his increased expenditure of energy. If, however, the carbohydrate and fat of his food is insufficient for his caloric needs, protein will be broken down for its 60 per cent carbohydrate fuel value and consequently his protein requirement will be greater than one gram per kilogram. This is expensive fuel both economically and physiologically. Carbohydrate and fat are protein spacers, and of the two, carbohydrate is safer for a diabetic than fat.

The carbohydrate and fat content of the diet may vary with the requirements of the patient, whether we desire him to gain, lose or maintain weight. Even these calculations may be avoided by adopting a standard beginning diet. This is the practice in most hospitals today.

The beginning diets employed at St. Luke's Hospital are

TABLE I

### BEGINNING DIABETIC DIETS\*

		C	P	F	Calories
Adults		130	65	50	1230
Children	4 years	90	45	20	720
	8 years	100	60	30	910
	12 years	110	75	40	1100

\* These should be increased to maintenance requirements as soon as the diabetes is controlled. A maintenance diet is one which keeps a patient at his ideal weight, and it differs for each individual. The patient's weight is the only reliable guide to his caloric needs.

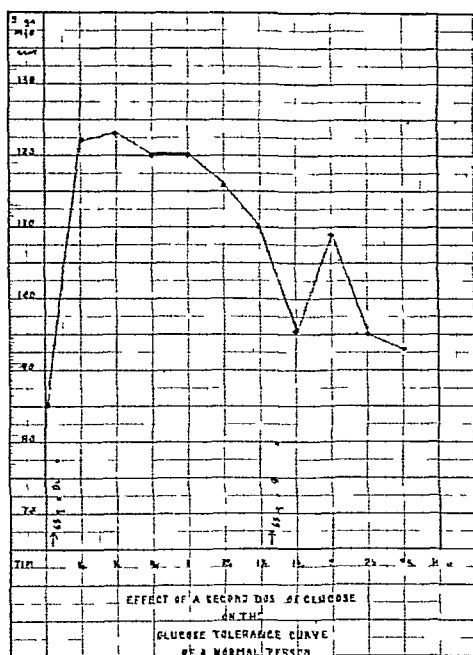


CHART I

These are beginning diets only and are usually less than the patient needs to maintain weight. When the diabetes is controlled on this diet, how are the maintenance requirements of the patient determined? Again it is a simple matter. Instead of making elaborate calculations of the patient's theoretical caloric needs, we simply weigh him once or twice weekly. If he gains weight the diet is too much, if he loses, it is too little, and if his weight remains stationary, it is sufficient. The scale on which the patient is weighed is one of the most essential instruments in the treatment of his diabetes.

The *distribution* of the food throughout the day is equally as important as the amount consumed. *All diabetics should eat between meals.* When employing protamine insulin, these supplementary feedings are especially necessary in order to avoid insulin reactions. Not only do these extra feedings prevent insulin reactions, but, by stimulating the glucose metabolizing apparatus of the body, they enable the body to handle the following meals more effectively.

This stimulating effect of carbohydrate is shown very nicely when a glucose tolerance curve is done with two doses of glucose instead of one. If a second dose of glucose is ingested during the descending arm of

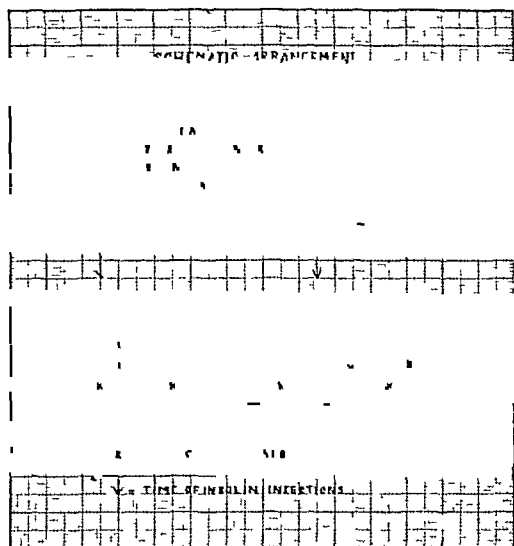


CHART II

the curve it will cause less of an elevation of the blood sugar than the original glucose feeding (Chart I)

The fact that carbohydrate given at one time will act as an antidote to insulin while at another it will stimulate insulin production, appears to be contradictory. The reason, of course, is that carbohydrate does not act as a stimulant to insulin production until it has raised the blood sugar to a certain critical level.

In addition to this distribution of the food into six feedings, it has been found that if the three meals themselves be divided in certain definite proportions the maximum carbohydrate load will correspond more closely with the maximum action of insulin (Chart II).

It is important, especially at the bedtime feeding, to give the carbohydrate in a slowly absorbing form, such as crackers, milk, cereal or even vegetables, rather than orange juice. Otherwise its buffer effect may take place too rapidly to prevent hypoglycemia in the early morning hours.

It is clear, therefore, that this distribution of food and insulin is not an arbitrary one but is based on a knowledge of the properties of the two types of insulin employed. It is theoretically sound, and yields practical results in diminished glycosuria and fewer insulin reactions.

## FLUID DIET

TABLE II

## THE "B &amp; O" DIET

To be used during acute infections, following coma treatment and postoperatively

C 122—P 21—F 7—Calories 635

7 00 A M	Orange juice, 6 ounces
9 00 A M	Buttermilk, 6 ounces
11 00 A M	Orange juice, 6 ounces
1 00 P M	Buttermilk, 6 ounces
3 00 P M	Orange juice, 6 ounces
5 00 P M	Buttermilk, 6 ounces
7 00 P M	Orange juice, 6 ounces
9 00 P M	Buttermilk, 6 ounces

Skimmed milk may be substituted for buttermilk, and ginger ale for orange juice with no change in food value

Water, clear broth and tea or coffee (without cream or sugar) are allowed as desired  
Insulin is given by the "color formula" with this diet

Whenever a diabetic has a fever he must go on a *fluid diet*. Any fluid diet will answer the purpose provided the feedings are given frequently. The one which has been used successfully at St. Luke's Hospital for the past ten years consists of six ounces of buttermilk alternating with six ounces of orange juice every two hours from 7 A M to 9 P M. Additional feedings are given at twelve midnight and 4 A M if the patient is awake. If the patient dislikes buttermilk, skimmed milk is given instead. Ginger ale may be substituted for orange juice. This diet should be given whenever the patient from whatever cause cannot take solid food. It is used postoperatively, during acute infections or even for seasickness. This diet, with the night feedings, contains about *130 grams of carbohydrate, 25 grams of protein and practically no fat*. Being low in fat it is an ideal diet for combating acidosis which usually accompanies the conditions for which this diet is prescribed. With this diet insulin is given every two to four hours by the "color formula."

TABLE III

## COLOR FORMULA FOR GIVING INSULIN

The urine is tested with Benedict's qualitative solution every two or three hours and insulin given as follows

- If the test is orange give 15 units of insulin
- If the test is yellow give 10 units of insulin
- If the test is green give 5 units of insulin
- If the test is blue give 4 ounces of orange juice

(Do not continue giving orange juice according to this formula if the test remains blue)

Let it be emphasized again that the management of the diet of a diabetic is extremely simple once we accept the principle that the responsibility of its calculation be transferred from the physician, who is not trained to do this work, to a dietitian or nurse or even another diabetic patient who is trained to do it. The above two types of diet are the only ones that need concern a physician treating a diabetic patient. One diet can be expressed by a prescription of three figures (keeping within the limits laid down in the principles of treatment) and the other is prescribed by the glassful.

### INSULIN

The introduction of protamine insulin constituted a distinct advance in the therapy of diabetes. But *protamine insulin is not a substitute for standard insulin* except in mild cases. One thing protamine insulin has done is to reduce the necessity for multiple doses of insulin in severe diabetics. For a *mild diabetic*, one dose of protamine insulin alone in the morning is sufficient. A *moderately severe diabetic* will require both protamine and standard insulin before breakfast. A *severe diabetic* needs an additional dose of standard insulin before supper. Young children may require an additional dose of standard insulin at lunch time.

A characteristic effect of protamine insulin, with or without standard insulin, is a flattening out of the twenty-four hour blood sugar curve, eliminating the peaks that occur in mild diabetics not taking insulin and in severe diabetics even with frequent doses of standard insulin (as is shown in the accompanying charts).

The importance of abolishing wide daily fluctuations of the blood sugar is emphasized when we examine its effect on the daily nitrogen balance. Wilder has shown that when the blood sugar rises above the renal threshold there is an increased excretion of nitrogen in the urine with a consequent loss of amino acids. The amino acids are the very substance from which cellular protoplasm is formed and are the precursors of the immune bodies which provide resistance to infection. This loss of amino acids undoubtedly contributes to the lowered resistance to infection of uncontrolled diabetics and the stunted growth of improperly treated diabetic children.

How does one determine the initial dose of insulin for a diabetic patient? At best the beginning dose is a guess. A safe dose with which

TABLE IV  
METHODS OF INSULIN ADMINISTRATION

1	For Regulation—									
10	Protamine insulin									
	5—5—5—	Standard insulin								
	Urinalyses—									
	Feedings—									
	Standard Insulin—									
	Protamine Insulin—									
	before meals									
	four daily									
	three meals and three supplementary									
	feedings									
	dosage changed daily on the basis of the									
	previous day's urinalyses									
	dosage changed every three days as indicated									
	by the 7 A M urinalysis									
2	Acidosis—									
10	Protamine insulin									
	AM	AM	PM	PM	PM	M	AM			
	7	10	1	4	7	10	12	4	Standard insulin	
	Urinalyses—									
	Feedings—									
	Standard Insulin—									
	every three hours									
	every two hours									
	dosage changed every three hours on the									
	basis of the color formula									
	as above									
	Protamine Insulin—									
3	Coma—									
50	Protamine insulin									
	50	40	30	20	20	20	Standard insulin			
	Urinalyses—									
	Feedings—									
	Standard Insulin—									
	every half hour									
	glucose and saline intravenously									
	twenty units every half hour until urinalysis									
	is "green" or blood sugar is 200 mg per									
	cent									
	fifty units as the initial dose After that									
	once daily as in acidosis									
	Protamine Insulin—									

to begin a known adult diabetic is ten units of protamine and five of standard insulin before breakfast and five units of standard insulin before lunch and supper. For young children the dose should be five units of protamine and three of standard insulin before breakfast and three units of standard insulin before lunch and supper. They are expressed respectively as  $^{10}5-5-5$  and  $^53-3-3$ . These doses are increased or decreased until the maintenance dosage is arrived at. The criteria by which the insulin is increased or decreased are the four daily urinalyses, which will be discussed later.

## COMPLICATIONS

### 1 Insulin Reactions

Insulin reactions occur both with protamine and standard insulin. Reactions with standard insulin are apt to occur from two to five hours after injection. The treatment is ten to twenty grams of carbohydrate in the form of orange juice or sugar. If the patient is unconscious, 1 cc of adrenalin chloride should be given subcutaneously, and glucose should be given intravenously or by stomach tube.

Reactions with protamine insulin usually occur from twelve to

twenty-four hours after injection. Because the reduction of the blood sugar is gradual over a relatively long period of time, the body becomes accustomed to the hypoglycemia and symptoms frequently do not appear until the blood sugar has fallen to 50 mg per cent or lower. These reactions are more severe and prolonged than reactions due to standard insulin. The treatment is the same as for reactions due to standard insulin except that carbohydrate should be given repeatedly for a considerable time, ten to twenty grams every half hour for three or four hours or until the symptoms disappear.

### 2 *Acidosis and Coma*

Many good clinicians are now employing protamine insulin in the treatment of diabetic acidosis. In coma, an initial dose of fifty units is given followed by frequent and repeated doses of standard insulin in the conventional manner. In milder degrees of acidosis such as occur in acute infections, a morning dose of ten to twenty units of protamine insulin followed by standard insulin every two or three hours will add to the effectiveness of the standard insulin and shorten the period of acidosis. The dosage of either type of insulin must of course be controlled with frequent blood or urine analyses or both.

### 3 *Gangrene*

After acidosis and coma, the most important complication of diabetes is gangrene. This invariably occurs in the lower extremities and differs in no way from arteriosclerotic gangrene. In fact it is arteriosclerotic gangrene which occurs earlier in the diabetic than the non-diabetic.

A beginning gangrene of the toe will sometimes clear up with rest in bed and control of diabetes alone. Should the gangrene persist, surgery is indicated. An open sore of six weeks duration suggests the presence of osteomyelitis. X-ray of the toe will usually show bone destruction.

The question is whether to resort to radical or conservative treatment. In general, if the foot is warm with no pain and there is good pulsation of the arteries, conservative surgery is indicated. A moist gangrene with spreading cellulitis and lymphangitis up the leg calls for more radical surgery.

The management of the usual *acute surgical emergencies*, such as appendicitis, in a diabetic patient is a special problem. These cases are usually admitted in severe acidosis, and if possible two or three hours should be devoted to controlling this condition before operating. This

TABLE V

## TREATMENT OF DIABETIC COMA

The immediate and indispensable need is fluid and sodium. These are more essential at first than insulin, because insulin is ineffective until the body fluid is restored.

*Conditions to Combat*

A Dehydration and peripheral circulatory failure (shock)

B Acidosis

1 *Dehydration and Circulatory Failure*

- 1 Physiological saline intravenously 1000-5000 cc—glucose 5 per cent should be included in the first infusion
- 2 Saline by rectum—6 ounces q 3 h
- 3 Gastric lavage
- 4 Clear broth, tea, coffee or water by mouth
- 5 Keep patient warm

b *Acidosis*

- 1 *Insulin*—one unit per kilogram of body weight as first dose. Then insulin is given in diminishing doses every half hour until the urine is "green" by Benedict's test or the blood sugar is 200 mg per cent

50—40—30—20—20—20

The urine is tested every half hour

- 2 *Glucose* is indicated

does not add to the surgical risk but reduces it, for these patients are often dehydrated and in shock, and measures directed toward overcoming the acidosis will at the same time combat the state of shock.

A blood sugar and CO<sub>2</sub> determination should be done at once. During the hour it requires to report on these, an infusion of 1000 cc of saline is given with fifty grams of glucose and twenty-five units of insulin. After this the urine is tested every half hour, and twenty units of insulin given each half hour until the urine test is "green." In this way 105 units can be given in the two hours preceding operation, and the patient will be a much safer operative risk. A similar infusion after the operation with the same glucose and insulin is often helpful. As soon as fluids are allowed by mouth, the patient is placed on the fluid diet and insulin is given every two or three hours by the "color formula."

## SIGNIFICANCE OF LABORATORY FINDINGS

The analysis for sugar of a single specimen of urine or even of a twenty-four hour specimen is of no value as a guide to insulin therapy. It merely proves that the patient has glycosuria at a particular moment or sometime during the twenty-four hours. What we want to know is after what meals is the patient spilling sugar? *In order to give insulin at the time it is needed and to avoid reactions, at least four daily analyses must be performed.* For the ambulatory diabetic it is sufficient to collect and analyze qualitatively a single specimen before breakfast and from

one to two hours after each meal. The before-breakfast specimen will reflect the effect of the protamine insulin given the previous day before breakfast. The forenoon, afternoon and evening specimens will detect the presence of glycosuria resulting from the corresponding meals and will indicate the necessary distribution of standard insulin if any is required. Before altering the insulin dosage a twenty-four hour record of these analyses is necessary. Therefore the *insulin dosage for any given day is determined by the analyses of the previous day*. It is essential to make these separate analyses every day while the insulin dosage of the patient is being adjusted. When the patient is stabilized they can be done every two or three days or even once weekly.

The urinalysis alone, then, provides a sufficient guide for controlling glycosuria or hyperglycemia. For detection of hypoglycemia, however, the urine analyses are only suggestive. With a sugar free urine hypoglycemia may or may not be present. A blood sugar analysis therefore *is* necessary to detect an impending reaction due to hypoglycemia. Indeed the chief function of a blood sugar analysis today is to prevent insulin reactions.

Again, as in urinalyses, a single blood sugar determination is of comparatively little value. In order to discover the times at which insulin reactions are most likely to occur, a *blood sugar curve* should be done. That means testing the blood for sugar several times during the day. At least four tests should be made: 7 A M, 11 A M, 5 P M, 11 P M.

This blood sugar curve need be done only once and that is when the patient has become regulated, so far as this can be determined by urinalysis alone.

In conclusion, I should like to emphasize that one needs to be familiar with only *one* diet on which to start any diabetic patient. This diet can be expressed by a prescription of three figures. One can even begin on the fluid diet, which is measured by the glassful. *Subsequent changes in the diet depend upon the weight of the patient*. The initial insulin dosage should be conservative. *Subsequent changes in the insulin dosage are determined by the four daily urinalyses*. Blood sugar tests are unnecessary while sugar is showing in the urine. When sugar disappears from the urine, the insulin dosage should be lowered enough to give an occasional "green" test. This will prevent insulin reactions. A blood sugar curve at this point is extremely helpful, but not mandatory.

# HIERONYMUS MUENZER AND OTHER FIFTEENTH CENTURY BIBLIOPHILES\*

E P GOLDSCHMIDT

London

IF IT is true that we can learn a great deal about a man by glancing over the bookshelves in his library, it is all the more certain that when by some kind chance the entire book collection of a scholar of 500 years ago has been preserved for us through the centuries, we will be able to gather quite a good deal of valuable knowledge about him, his way of life, his interests, and his work, by studying the volumes of his library

It was my good fortune over twenty years ago, when I was working for the incipient *Gesamtkatalog der Wiegendrucke*, to stumble upon such a survival, the library of a XVth century physician who lived at Nuernberg and died in 1508. It was in the library of Prince Dietrichstein at Nikolsburg, Moravia, that I found, while cataloguing a collection of about 600 incunabula which had stood there undisturbed since the XVIIth century, that over and over again in the covers of the ancient bindings, the same owner's inscription in red ink kept on recurring, and it was soon obvious that some XVth century collection was here incorporated in its entirety. As I went on with my work, I kept track of these volumes and finally found that out of the 600, about 150 volumes bore this entry "*Hic liber est mei Hieronymi Monetarii de Feltkirchen, artium et medicinae doctoris, quem mihi comparavi Nuremberge anno Domini 1482*"—or something like that.

Naturally, I not only made a list of these books which had remained so conveniently together, but I tried my best, off and on through the last twenty years, to find out all I could about this Dr. Monetarius, who he was, where he lived, and what he did. After all sorts of delays and vicissitudes, and after the Nikolsburg library has ultimately been entirely dispersed and scattered all over the world, I am now at last about to publish a little book on the man and his library, and thus to preserve the record at least of an interesting survival which unfortunately has not

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itself been able to withstand the upheavals of these post-war years

I should like to tell you a little about this Dr Hieronymus Muenzer or Monetarius, about the books he owned, about his travels, of which he left us such an interesting record, and finally, in order to show that such a standard of culture, of learning, and of book-collecting was by no means so very exceptional, about some other German physicians of the same period whose books have survived to our day

Muenzer was born exactly 500 years ago at the town of Feldkirch in Vorarlberg, which many of us know as the frontier and passport-control station for travellers entering Austria from Switzerland I am precise, for it is by no means *on* the frontier between Austria and Switzerland, since at that exact spot a strange oversight of history has spared to survive to this very day the independent principality of Lichtenstein So when you leave Buchs in Switzerland and arrive in Feldkirch in Austria, your train has without warning and without stopping traversed the entire breadth—about four miles—of this very ancient state

Muenzer came of a good family, we may presume, for his sisters married quite eminent people, but they were poor, for he tells us in one of his extant notes that it was by the help of "pious people" that he was enabled to study He matriculated at Leipzig University in 1464 and took his M A in 1470, he remained another four years as a junior lecturer in the Arts course and not only maintained himself but even managed to save 400 florins in that way We may note that Muenzer was comparatively old at twenty-seven when he first began his university studies at that time it was quite usual for students to enter at the age of fifteen There is a manuscript in Muenzer's library which proves that he had begun to turn to medicine before he left Leipzig, a folio volume on paper containing an extensive "Herbarius," Bernardus de Gordonio's "*De ingenis curationum*," a brief "*Bona Anothonna*," and other medical texts, in the front cover he has noted "*Iste liber medicinalis est mei Hieronymi Monetarii de Feldkirchen artium et medicine doctoris quem mihi compariavi in studio lipzensi anno 1470*" It is now in the Wellcome Museum in London

However, it was at that time considered an established fact that a first rate medical training could not be obtained in the comparatively new German universities, and only the Italian M D degrees of Bologna, Padua, and Pavia gave a medical man the prestige that enabled him to get into the first rank That this state of affairs was quite officially

recognized, we can prove from a resolution passed in 1463 by the Faculty of Arts of the University of Heidelberg, by which leave of absence was granted to a Magister Nicolaus Swarczunz to go and study in the medical faculty "*que non vigeret in Almania*," "Which was not flourishing in Germany" We happen to know how it became possible for Muenzer to continue his medical studies at Pavia In the summer of 1470 when Muenzer took his M A degree, a young Nuernberg patrician, Anton Tetzl, matriculated at Leipzig, and it was as this boy's private tutor, and at his expense, that Muenzer could go to Pavia in 1476 and complete his medical studies there, taking his M D in 1478

Of Muenzer's Pavia period some interesting relics survive among his books For example, one of his actual medical lecture notebooks containing the "Anatomy" of Mundinus, and considerable excerpts from Galen and Haly Abbas, "*consilia*" of his teachers, Antonio Guaineri and Ambrosio Binasco, and other matters That he did not neglect the practical side of therapeutics for his theoretical studies is shown by a verse he entered on the flyleaf

*"Dum dolet infirmus/medicus sit pignore firmus*

*Nam si post queris/querendo hostis eris*

*Non didici gratis/hec musa sacra Hippocratis*

*Egis (imp ?) serviet absque dativis "*

(While the patient is in pain let the doctor make sure of his reward  
For if you ask for it afterwards you will only make yourself unpopular  
by asking

It is not without cost that I have learned the venerable science of  
Hippocrates

But impecunious patients he may serve without remuneration )

This interesting volume is now in the library of Dr Harvey Cushing at New Haven It is from Pavia also that Muenzer brought back some of the fine books which went to form his library, and we may assume that it was there that he first became infected with the book-collecting bacillus and that the nucleus of his library was brought together Of course, this period, 1477-8, in which he first became financially able to spend some money on books, coincided with the first great burst of activity of the printers which brought books within the reach of people with moderate incomes

At Nikolsburg, I found at least ten volumes in which Muenzer had noted his purchase as a student at Pavia, but there are at least about

fifteen or twenty that fall in this period. There is an Avicenna "Canon" 1473, a Saliceto of 1476, two works of his teacher Guainerius "De Febris," and "De Matricibus," 1474, the "Pandecta Medicinæ" of Sylvaticus. The "Antidotarium" of Falcutius, bound with the Albucasis, both printed by Jenson in 1471 are now in the Boston Medical Library. But even then Muenzer did not by any means confine himself to medical books. There are his *Juvenal* of 1474, with extremely amusing marginal notes, now in the Yale University Library, a Lucan, a Quintilian, a Diogenes Laertius, a Sallust, the "Cosmography" of Aeneas Silvius. His first book of all, perhaps, is the Aristotle, "De Animalibus," Venice 1476, in which he made this vivid entry recording its acquisition.

"In the year of the Lord 1476, in the last days of December, when we celebrate the birth of our Saviour and indulge in all sorts of games and pastimes, I obtained this very fine book at cards and dice. By the kindness of certain noble students of the German nation who were then studying in the faculty of Civil Law in the famous University of Pavia, at the time when Galeazzo Maria, Duke of Milan, the fifth to hold the tyranny in that principality, was killed by the dagger of a poor devil at Milan."

Immediately after leaving Pavia, the newly promoted M.D. again no doubt through the influence of his pupil, Tetzl, obtained permission to settle and practise at Nuernberg, and the appointment as one of the "Physici" of the city of Nuernberg, which I suppose corresponded to something we in England call, "Medical Officer of Health." We happen to have one of Muenzer's official reports to the City Council, made within a year of his establishment, when he gave his opinion on their enquiry whether the practise of using sulphur to clarify wine was detrimental and whether it should be prohibited. Muenzer's consilium dated 27 October 1479, makes a great display of quotations from two dozen authorities, from Galenus and Avicenna to Gordonius and Arnoldus de Villanova, and leaves the question open. It has been preserved for us through the zeal of his friend, Hartmann Schedel (of whom more anon) in a Munich manuscript, *codex latinus monacensis 456*.

In 1480, Muenzer got married and his only child, his daughter Dorothea, in 1499 became the wife of that Hieronymus Holzschuher whose honest face is familiar to so many people because his portrait by Albrecht Durer is one of the best known pictures in the world.

In 1483, a serious outbreak of the plague overwhelmed Nuernberg,

and before it was over caused about 4000 deaths in less than a year. The council immediately at the start of the epidemic, required its four appointed physicians, Hermann and Hartmann Schedel, Johannes Kraemer, and Hieronymus Muenzer to give out a kind of official notice of advice to the population how best to preserve themselves from the pestilence. This *consilium* again is extant, also through the industry of Hartmann Schedel, in *codex latinus monacensis 441*, and is quite an interesting document for our knowledge of XVth century hygiene.

"First and foremost," we read, "all the medical authorities recommend flight and to escape as soon as possible from the city and region where the pestilence is reigning, and to go far away and not to return but slowly when the poisoned air is properly clean again." For those who for one reason or another cannot escape from the city, the doctors recommend a number of prophylactic measures such as, fumigations, certain pills which you can obtain at the chemists, certain special powders also obtainable at the druggists, a special draught, etc., all these being put forth obviously without any profound conviction and seemingly more out of a friendly regard for the kindred profession of pharmacy. Anyhow, Muenzer himself, in spite of his position as official *physicus* to the city of Nuernberg, followed his own best advice and departed. He left Nuernberg on the 12th of September 1483 and went to Italy, visited Pavia again, then Bologna, Florence, Rome, and Naples, and came back in January 1484, quite pleased, as he records, to find his wife, child, and all his servants quite safe and sound on his return. He is quite frank about his motive in the brief record he has left of this little trip.

"In the year 1483, struck by the fear of a contagious pestilence, I thought that those are least likely to die in a war or in a plague who are not in them, and so, having decided to escape, I left Nuernberg in September," and so on.

Our Doctor Muenzer had been doing well in his medical practice. He tells us that in the first year he made over 500 florins, which must have been very respectable, and he could afford not only to travel but to buy some very fine books. Quite a number of them have survived and he notes in their covers that he bought his Gordonius, "*Lilium Medicinæ*", at Naples, his Claudianus and Solinus at Rome, his Boccacio, Theophrastus, and others at Milan.

In the following year, 1484, this time apparently without any pestilential inducement, the doctor made another little tour down the

Rhine to Aix-la-Chapelle and Belgium, allowing himself only eighteen days altogether for the trip. It is obvious that Muenzer enjoyed travelling in spite of the discomforts of journeying by mule and hack and the chances of indifferent accommodation for the night.

For the next ten years, for all we know, he seems to have remained at Nuernberg, attending not only to his practice and to his library, but also to quite extensive and definitely successful business enterprises. We learn about these trading engagements, mostly in partnership with his brother Ludwig, from the brief statement on his financial position which he drew up in 1507 shortly before his death and which is preserved in the library of the Germanic Museum at Nuernberg. That his friends looked upon him as a business-man as well as a physician, can be gathered from a letter of thanks addressed to him by Sixtus Tucher in which he hopes to hear from him "*cum a tuis mei caturae ac medicinae negocus vacaveris*" (when you can spare the time from your medical practice and business affairs).

In those busy years his library was steadily growing, as we can well observe by noting the dates of purchase which he generally, though not always very reliably, wrote inside the covers of his books. His interests, as we can gather from these, remained very general, and in fact it is not the field of medicine that predominates among these acquisitions after 1484. There are two special predilections we can deduce from his books. He became an enthusiastic admirer of the Platonic philosophy which was gaining such a wide following among the humanists of the late XVth century. This vogue was partly a reaction against the over-subtilised and academically over-elaborated Aristotelianism which had dominated in the European universities for two centuries, but certainly also due to the wonderful appeal the newly rediscovered and recently translated works of Plato and Plotinus made to the men to whom they came as fresh novelties, not as old textbooks read as a matter of duty in class. Muenzer obtained the first Plato in Ficino's Latin translation, of course (the Greek was not printed till 1513, and Muenzer could not have read it even if it had been available) immediately on its publication, from Florence in 1487. The Plotinus of 1492 also came to him immediately after its appearance "*ex Florentia Tusciae civitate anno Domini 1493 Ob quam praeclarus et plenus philosophia hic liber est*." And in 1494 he makes an even more enthusiastic and fervent entry in his "*Mercurius Trismegistus*," a late Neo-Platonist treatise of mystical philosophy, which

in Muenzer's day was erroneously supposed to be of much greater antiquity than either Plato or Aristotle

Muenzer's predilection for this type of philosophical reading matter can most strikingly be proved from his note at the end of Aristotle's *Politics*

"This most noble book on the State written in beautiful language and full of weighty sentences, has been read through by me Hieronymus Monetarius *utriusque medicine doctor* I read it through, I say, for the sake of recreation, in the month of May 1499, when I was suffering of a dangerous disease, and used to alleviate the intolerable pain by this very agreeable reading at Nuernberg "

The other favourite study of Dr Muenzer, which also shows up clearly from his library, his fine Ptolemy (the rare first edition) his Solinus, his Mela, Aeneas Sylvius, and other cosmographical writers, is *Geography* In geographical science indeed we have evidence of an interest carried beyond mere quiet study, and manifesting itself actively both by original literary work in this field, and in the doctor's unquenchable desire for travel and the visiting of unknown lands

Nuernberg in those days was a great commercial center, one of the most important on the continent, ranking with Venice, Florence, Antwerp, Augsburg, Lyons, and Bruges The Nuernberg patricians, who sat in the senate of their self-governing city-republic, were many of them great merchants with world-wide interests in every market from the Baltic to the Mediterranean, from Russia to Portugal, many of them had been acting as agents for their family firms in remote countries, and they were wont to send their sons out to foreign ports and fairs to watch their interests To this type of man, the scholar who could write neat Latin verse, or make an elegant speech, or write a well-phrased letter in Latin would mean very little, but a man who from his book-learning could produce knowledge of the remote countries of the globe, of the problems of navigation, and of the courses of the stars, would give an impressive proof that something worth while was to be gained from study We have ample evidence that in the Nuernberg of the 1480's and '90's Dr Muenzer was looked upon as the great authority in matters geographical And when his friend, Hartmann Schedel, prepared his great Nuernberg Chronicle of 1493, that well-known encyclopedia of historical knowledge and the most famous picture book of the XVth century, it was to Muenzer that he turned for help to bring the geo-

graphical section of the work fully up to date I have been able to prove by examining the extant original manuscript at Nuernberg and Schedel's own copy of his book preserved at Munich, that Muenzer is responsible not only for extensive corrections and additions to the geographical section at the end, such as, for instance, the passage on Martin Behaim's voyages along the coast of Africa, but that the map of central Europe added on the last pages, is his and not Schedel's work

Muenzer's personal friendship with Martin Behaim, the seafarer, did not only lead him to supply the account of his voyage in the Schedel Chronicle, and very probably to collaborate in the making of Behaim's famous globe of 1492, which is still extant at Nuernberg, it ultimately made him undertake his greatest personal venture, his journey to Spain and Portugal in 1494-5, of which he has left us such an interesting account. Behaim himself is rather a mysterious and unsatisfactory person. The younger son of one of the foremost Nuernberg patrician families, he ran off to sea as a boy. He certainly did succeed in accompanying Diogo Cano and his Portugese sailors on a voyage along the African West Coast in 1484, and was knighted by the King of Portugal on his return. That, however, is all we know of his practical experience as a navigator, and on his globe, however beautiful and picturesque it may be, there is little evidence of any unusual knowledge either of Africa or any other part of the world. It is quite obvious, though, that he succeeded in impressing his Nuernberg friends with his tales of adventurous exploration, and, on the other hand, the Portugese authorities with his claims to profound astronomical and mathematical learning, for he was made a member of the *Junta dos Mathematicos*. Anyhow, whether he was an impostor or not (and Muenzer's experiences tend to show that he was), he induced Muenzer to write a very remarkable letter to King John of Portugal, dated Nuernberg, 14th July 1493. In this letter, the doctor recommends that the King should send out an expedition to sail westwards across the Atlantic Ocean and so to reach the Indies and Cathay, and he suggests Martin Behaim as a suitable captain for such an enterprise. He supports his theory with quotations from Aristotle, Seneca, and Pierre d'Ailly, and points to other indications, such as the existence of elephants both in India and in Africa, and the driftwood washed up by the sea on the western shores of the Azores, to prove the proximity of land in the west.

This extraordinary letter, which has such striking similarities to the

famous letter Toscanelli wrote in 1474 to a Portugese friend, would indeed have made our Dr Monetarius a famous man, if it were not unfortunately a fact, which he could not know on July 14th when he wrote his letter, that Columbus had returned from his first voyage on March 4th. And even if he had known of Columbus' discovery of a few more islands in the western sea, this would not have affected his views any more than Columbus' own, for even on his third voyage the explorer was still endeavoring to reach Cathay, unaware that what he had stumbled upon would prove such a serious obstacle to that voyage.

Anyhow, it is clearly not unconnected with such projects that Muenzer in the following summer, 2nd of August 1494 to be exact, set out on his journey to Spain and Portugal, and had an audience with King John at Evora in November. But although he has left us a very detailed account of these interviews—he was four times asked to dine with the King—there is not a word on Behaim in this or anywhere else in the "Itinerary," and it looks as if that name, which seemed to him so powerful at Nuernberg, had lost its glamour when brought out at the Portugese court.

I obviously cannot give now an adequate or even a brief account of the varied and vivid interest of Muenzer's travel diary, in which he has left us a record of his journey from Nuernberg via Switzerland, Lyons, the Rhone valley, Perpignan, Barcelona, Seville, Madrid, Granada (quite recently conquered from the Moors), to Lisbon, and back via Sant' Iago de Compostella, Toulouse, Poitiers, Paris, Bruges, Cologne, and so to Nuernberg. He returned about Easter, 1495. It is a most valuable document, and it is astonishing that it should not hitherto have been published in its entirety. The principal and no doubt most exceptional portion of it, that relating to Spain and Portugal, was printed in the original Latin in the "*Revue Hispanique*" in 1920, and after that in both a Spanish and a Portugese translation, and it amounts to about two-thirds of the whole text which occupies 416 pages of the Munich manuscript in which it has survived. The rest—that is the journey from Nuernberg to the Spanish frontier and back from the Pyrenees to Nuernberg—has not yet been edited, and I am hoping to see it printed this year in a French periodical, "*Renaissance et Humanisme*." Of course, although unedited, the manuscript has by no means remained unknown, it has been frequently used and referred to, and little extracts have been given ever since Kunstmann, in 1854, wrote about it in the *Transactions of the*

*Bavarian Academy* and particularly quoted from it all that refers to the Spanish and Portugese discoveries Naturally, with his keen interest in geographical matters, Muenzer had noted a good deal which he had heard about the overseas countries, especially West Africa, from navigators and merchants, but unfortunately we seem to have lost a special discourse of his, "*De insulis*," to which he refers, but which was either never written, or has gone astray It is interesting to note that one of the people he met in Madrid and who gave him a letter of recommendation on his way, was the Benedictine monk, Bernard Boil, who accompanied Columbus on his second voyage

It does not seem that Muenzer brought back any books with him from Spain or Portugal Anyhow none have survived at Nikolsburg, but he did buy some books for his library in Paris where he remained for ten days in the Spring of 1495 His account of Paris is one of the most detailed we possess of that period and should be most valuable for the local historians and topographers of that city, it is odd that it has never yet been printed

Not much remains to be said on the remaining years of Muenzer's life, he seems to have continued quietly at Nuernberg, doctoring and collecting books until his death in 1508 Shortly before that, he visited his native town, Feldkirch, and gave a considerable part of his library to St Nicholas Church there, a donation of which a few volumes have indeed survived, but of which we have a complete list in the Feldkirch archives, which enables us to complete the total of Muenzer's library with at least the titles of the books which have disappeared On the same occasion, Muenzer established certain charitable trusts at Feldkirch, and an annual Mass which he endowed was indeed punctually said on his anniversary until quite recently

Muenzer's *Itinerary* has not come down to us in his autograph, the only copy we possess of it, the Munich manuscript, is written in the hand of his friend, Hartmann Schedel, the author of the "*Nuernberg Chronicle*" You may have noticed that, again and again, I have had to refer to things like Muenzer's report on the adulteration of wine or on the measures against the plague, as surviving in some manuscript written by Schedel This may give you just an idea of the immense amount of most varied material whose survival and existence we owe to the industrious pen of Hartmann Schedel Schedel, Muenzer's close colleague as official *physicus* of the city of Nuernberg, was indeed a prince of book-

collectors and a champion copier of books. He not only bought all books printed or manuscript he could get hold of, but, with indefatigable zeal, seized every opportunity to copy anything he could borrow or otherwise obtain. Schedel's famous library has been luckier than Muenzer's, about 350 manuscripts and 500 to 600 printed volumes of his still remain intact in the Munich Library, of which indeed they form the original nucleus. Comparatively few volumes have strayed from the fold, but one magnificent specimen at least is in the United States, his *Petrus de Abano* (Hain, No. 1), which is in Dr. Harvey Cushing's great library at New Haven. There also, you will find his copy of Nicolaus Leonicens' book on Syphilis (1497), but it is rebound in XIXth century calf. It is surely remarkable and significant that two prominent physicians in one city and at the same time should have been great bibliophiles, and in a way, I suppose, I must beg your pardon for speaking first and at such length about my own pet discovery, Hieronymus Muenzer, rather than about Schedel, whose library was about four times the size and infinitely more important than Muenzer's. But Schedel's library has been well known and indeed famous for many years, long before Stauber's monograph on "*Hartmann Schedel und seine Bibliothek*" came out in 1908, while the minor star, Muenzer, has remained undiscovered and unknown. And if I am now able to demonstrate the existence of a closely analogous though less overwhelming second humanistic library in a Nuernberg physician's house before 1500, this fact will help us to recognise that Schedel's was by no means an isolated phenomenon, and that indeed the possession of a noble library was a fairly normal distinction of a successful German medical man of the Renaissance period.

Hartmann Schedel, unlike Muenzer, was the son of a Nuernberg patrician family, born at Nuernberg in 1440, and the cousin of another book-collecting physician, Hermann Schedel, whose books he inherited. Schedel also began his studies at Leipzig, where he entered at the normal age of sixteen, and took his M.A. in 1461. He continued his medical studies in Italy, not at Pavia but at Padua, where he took his M.D. degree in 1466. He has left us an interesting account of an "Anatomy," the very exceptional dissection of a corpse, held at Padua on March 20th to 24th 1465, under Dr. Antonio Bernardi, not without mentioning that ultimately the corpse was buried with great reverence and ceremony. On his return to Germany, he held appointments as town physician at Noerdlingen and Amberg before he settled down to practise in his

native city in 1484. He died a few years later than Muenzer, in 1514.

Schedel's best known achievement, of course, is his famous "*Chronicle*," which was published by Anton Koberger at Nuernberg in 1493 in a double edition in Latin and in German, illustrated with the same woodcuts, 2000 copies of each being printed, this is a tremendous and unprecedented number for a XVth century publication. The whole enterprise was exceptional in its scope, and took about eight years to prepare, requiring the financial backing of two at least of the richest Nuernberg merchants. The illustrations alone—there are 1809 of them—took years to design and engrave, and we know that the studio of Michael Wolgemut, where Durer had been an apprentice, was fully occupied with them over a long period. The book as it came out, must be acknowledged to be a complete and successful realization of the object aimed at—a popular encyclopaedia of all historical knowledge, beginning with Adam and Eve, giving an account of all the Emperors and Popes, of the foundation of all the principal cities of the world, with a view of them, of all the most famous men and women, with their portraits if possible, and not only carrying the tale of events right down to the date of publication, but even providing six blank leaves for the entering of any further important happenings until the Day of Doom, this and the Last Judgment are again fully recounted and illustrated, bringing the gigantic work to an appropriate and final conclusion.

This magnificently illustrated "World-Chronicle" must not be judged as a piece of original historical research, nor must we tax Schedel with credulity for including in it all the ancient and mediaeval mythical lore about pagan heroes and Christian saints, about strange wild tribes, and the legendary origins of cities. His aim was to include everything that was popularly known and current about the world and its history, not to provide a scholarly reference book. And although the "Nuernberg Chronicle" is not unprecedented as a world chronicle, except in the magnificence of its production, and its models—Bergomensis' *Supplementum Chroniconum*, and the Luebeck *Rudimentum Noviciorum*, can clearly be recognised, it did require a scholar of wide reading and one with an encyclopaedic library at his disposal to produce the result.

From the fact that Hartmann Schedel undertook it, and from the efficient way he carried it out, we can deduce the bent of his interests. History and Archaeology were his favourite subjects, and what we can deduce from his work on the "*Chronicle*," we find confirmed when

we analyse the surviving books in his library. Of course, Schedel also had his shelves full of medical books and even a notable number of important and early medical manuscripts, the classics, the great Latin poets and prose writers both of antiquity and of the Renaissance were there in even more impressive completeness than in Muenzer's library. Indeed, the two collections are very similar in a way, and not only do we find copies of the same edition in both libraries in about 100 cases, which shows that the two friends had about the same source of supply but that they even employed the same bookbinders. Both Schedel's and Muenzer's books have mostly survived in their solid original bindings, and we see generally the same tools and the same decorations used on the majority of them. Roughly, one might say that Schedel had nearly every book that Muenzer owned in either the same or a similar edition, but he had far more than Muenzer, and it is just in the field of history, of old chronicles, annals, local and general historical works, that Schedel's library clearly outdistances Muenzer's. These historical books, moreover, were mostly not available in printed editions, and Schedel did not confine himself to purchasing such manuscripts, but with indefatigable industry wrote and copied such texts wherever he could find them. Of Schedel's 350 manuscripts now at Munich, probably nearly half are written in his own beautifully clear calligraphic handwriting. They form an unexhausted store of the most heterogeneous texts. In his eager zeal, Schedel not only copied entire historical works, or the monastic annals he found in the different abbeys, but letters, speeches, rhymes and verses, epitaphs and inscriptions, in fact almost anything which could be transferred by pen to paper. It is through Schedel's passion for writing that we have Muenzer's "*Travel Diary*," and Ciriaco d'Ancona's most precious collection of Roman inscriptions, mostly since destroyed, and an untold number of more or less important historical documents. Every year almost, one might say, some historical scholar manages to attract a little attention by publishing some text "hitherto unedited" from one of Schedel's manuscripts. If Schedel knew how much valuable historical material modern scholars have quarried from his manuscripts, and how they rather condescendingly smile at his tremendous "*Nuremberg Chronicle*," I do not think he would be either surprised or hurt. He consciously undertook the "*Chronicle*" as a work for the popular dissemination of historical knowledge, and would have been quite satisfied to let his immortality rest on his achievements as a book-collector and

antiquarian

Schedel then is a second and even greater book-collecting physician living at the same time and in the same town as Muenzer, another great bibliophile and doctor of the XVth century was born in the same little Alpine town as Muenzer Dr Ulrich Ellenbog Born at Feldkirch about 1430, he studied at Vienna where he took his B A , at Heidelberg where he graduated M A in 1455, and finally finished his medical studies at Pavia, under Guamerio and Matteo dei Gradi, taking his M D in 1459 He was thus at Pavia twenty years earlier than Muenzer, though not so very much older In 1460, he settled first in his native town Feldkirch to practise where he stayed till 1468, and where he wrote a treatise "*De balneis*" on medicinal baths, extant in a Vienna manuscript From 1472 on, he was appointed physician to the bishop and chapter of Augsburg, and resided there and at Memmingen until his death in 1499 Ellenbog's fine library of beautifully bound and kept books was bequeathed by him to the Benedictine abbey of Ottobeuern, where one of his sons had entered as a monk, and was kept together there until fairly recently It was dispersed, however, by the Munich book-trade within the last twenty years unfortunately before anybody had taken the trouble to note its contents while it was still intact It would be difficult now to track down all the scattered volumes of which one very fine specimen again is in Dr Harvey Cushing's library a "*Pharetra Doctorum*" printed by Mentelin without date, but before 1474, the date on which Ellenbog purchased it, as he notes in the front cover Being unable to say anything precise on the size and exact contents of Ellenbog's library, all I can affirm is that all his books I have ever seen (certainly over twenty) are finely printed big folios in their old white pigskin bindings, generally bearing a number of interesting marginal notes in his hand There are three points, however, we know about Ellenbog which make him a far from shadowy figure for us, and indeed a most interesting and significant personality Firstly, it was he, who on the foundation of the Bavarian University of Ingolstadt, was called upon to draw up the statutes of their medical faculty, but although he was appointed the first professor of medicine there, he does not seem to have cared for teaching, and returned to Augsburg in 1473 Secondly, he was not only a book-collector and a bookish person "*scribendi impiger*" and "*perpetuae lectionis*," as his son recorded about him, but he took a very important part in the establishment of one of the first printing presses at Augsburg,

that in the monastery of St Ulrich and Afra There is a volume containing five Augsburg *incunabula* in Cambridge University Library, bound up for Ulrich Ellenbog in 1476 and full of his autograph notes It is from these notes that Robert Proctor, in one of his "*Bibliographical Essays*" (1905) says "Ulrich Ellenbog and The Press of St Ulrich at Augsburg" has reconstructed the interesting facts about the collaboration of the abbot, the doctor, and a journeyman printer, in setting up this important press which printed among other things a 'Vincent of Beauvais'

Thirdly, there is among Ellenbog's medical writings—most of them small treatises of a few pages of the usual type—consilia about the plague and how to guard against it, "*De simplicibus*," "*De venenis*," and that sort of thing, one most remarkable pamphlet, a "*consilium*" dated 1473, in German, entitled "*Von den giftigen besen Tempffen un Reuchen der Metal, als Silber, Quecksilber, Bley und anders*"

"On the poisonous and noxious Vapours and Fumes of metals, such as Silver, Mercury, Lead, and others, which those of the noble craft of goldsmiths and other artisans who work with fire have to contend with How they ought to deal with them and how to get rid of their poisons"

This pamphlet, which got printed at Augsburg about fifty years after it was written, gives a brief but quite correct account of the injuries to health threatening metal workers who expose themselves to lead or mercury vapours, to nitric and other acids, and warns also against coal-dust and coal-vapours, it indicates a few simple remedies

However slight, this pamphlet is the earliest ever written in the field of industrial hygiene, and, as such, a remarkable starting-point of a discipline of tremendous importance and consequence Only a few years ago, in 1932, an English scholar, Dr C C Barnard, gave a translation of it in the *Lancet*

Clearly the fact that Ellenbog wrote such a pamphlet suffices to clear him of the imputation generally made against mediæval physicians, that they were men of mere book-learning, and shows him as a medical practitioner very fully alive to the problems of the world around him

If Muenzer could be characterised as the geographer and traveller among the XVth century German book-collecting doctors, Schedel as the historian and assiduous copyist, Ellenbog as the originator of industrial medicine, what is there we could briefly say to label Burchard

von Horneck, who left his splendid library with 183 manuscripts to the bishop and chapter of Wuerzburg in 1522.<sup>2</sup> He must have lived to a great age, for he graduated at Padua certainly before 1466 and in fact in 1509, Trithemius called him "grandævus." His books both printed and manuscript, are still largely preserved in Wuerzburg University Library, and hence the best notice of him will be found in a Wuerzburg dissertation of 1907 Ignaz Schwarz *Die medizinischen Manuscripte der Koeniglichen Universitaets-bibliothek Wuerzburg*. Few of them have strayed from there, sold as duplicates no doubt, but I do know two in the British Museum and an early printed Pliny in Dr Harvey Cushing's library. He owned all the standard Italian XVth century medical textbooks, either printed or in manuscript, and his Latin classics prove him to have been a keen reader of general literature on humanistic lines. He wrote quite a few little books—a poem, "*De ingenio sanitatis*," twice printed in the XVth century, and another poem on St. Patrick's Purgatory, also extant in print. Among those works of his which survive only in manuscript there is a puzzling treatise, "*Contra pestem inguinariam*," discovered by Sudhoff in the Salzburg library and dated 1475. If that date is right, this treatise is a first-rate piece of evidence for those who contend for an earlier origin of syphilis than the Naples-war of 1494.

But unfortunately, nothing about this good Dr Burchard von Horneck seems to be very reliable. He owned a manuscript of Camerino's well-known treatise about the plague, in which he has scratched out the author's name, substituting his own. In his fine manuscript of Montagnana's "*Definitiones terminorum medicinalium*," he has inserted a heading stating the book to be addressed "*ad dominum Brocardum de Horneck Alamannum scolarem novellum diligentissimum filium suum amantissimum*," it is certain, however, Montagnana was dead before Burchard came to Padua. So I am afraid one distinctive epithet we might give to Burchard von Horneck is that he was a liar.

An interesting group of fine incunabula from the library of another German doctor, Nicolaus Pol, is preserved now in the Cleveland Medical Library. There are about thirty of them, all in their old bindings, and bearing in their covers in very bold script the lettering "Nicolaus Pol Doctor 1494." In spite of a good deal of endeavour, both on my part and on that of others, we know comparatively little of this Dr Pol. He must have had a very fine and pretty large library, of which the Cleveland group is only a fraction. The majority of his books were housed in

an insignificant little Franciscan convent at Innichen (now San Candido) in the Southern Tyrol (now in Italy), immediately before they came on the market. But on my pre-war survey for the *Gesamtkatalog*, I also met them in quite considerable numbers in several monastic libraries of the Northern Tyrol, round Innsbruck, which accords with the attested fact that he was physician to the Emperor Maximilian I, who lived a good deal at Innsbruck. The date in his books is always 1494, whatever the date of impression, I now possess a book printed in 1511, with this inscription. This date can therefore not refer to the date of acquisition, and the most plausible explanation is that it is the date of his doctor's degree. Nicolaus Pol, Doctor 1494. But so far, his name, as far as I know, has not been found in any matriculation lists, and we do not know where he graduated. The only thing besides his fine surviving books, that we do know of Dr. Pol, is that he was the author of a treatise, "*De Morbo Gallico*", first printed in 1530. But we do not even know whether he was still alive when that book came out. I have never seen a book as late as 1530 with his ownership mark, in fact the 1511 book I just mentioned is, I think, the latest I have ever seen, and the majority of the Pol books are incunabula, including the splendid *Ketham* now in Cleveland.

We cannot possibly conclude a discourse on German medical book-collectors without at least a brief mention of the foremost of them all the greatest, the earliest, and, as the founder of a still existing great library, the most consequential. Amplonius Ratingk, the founder of the Collegium Amplonianum at Erfurt, and donor of its famous library. He belongs to a very much earlier generation than any of the preceding, having been born about 1363 at Rheinberg near Xanten in the Rhineland. So his earliest youth falls into the period before the establishment of any universities in Northern Germany, and he acquired the basis of his great learning and the earliest books for his library, at places like Osnabrueck and Soest where he also taught and copied manuscripts. His first teacher in Medicine seems to have been Tilmann von Syberg, court physician to Archbishop Frederick III of Cologne. The first university within the Holy Roman Empire was Prague in Bohemia, founded in 1363, and that is where Amplonius Ratingk took his bachelor's degree in 1385, his M.A. in 1387, it is likely that he also studied at Vienna, and it is certain that in 1401 he visited Italy, but only briefly.

Ratingk was associated with both the newly founded universities of

Cologne and of Erfurt from their very inception, and although he seems to have resided chiefly at Cologne, his principal benefactions went to Erfurt where he was Rector from 1393 to 1395, and where he took his M D In 1412 Ratingk founded his college, the Collegium Amplonianum, at Erfurt, and kept on adding to its endowment until his death in 1435

Amplonius Ratingk was a book-collector in the grand style, who not only kept a staff of copyists writing books for him continuously, but who went travelling about himself in the pursuit of books, we know, for instance, that he went to Bruges in Flanders to acquire a collection of forty manuscripts from the executors of the estate of a prelate, and we know that he bought books continually both from Paris and from Italy

From 1410 to 1412, before handing over his library to his college, he himself drew up its catalogue, which is still extant, as well as the books themselves, at Erfurt in the "*Amploniana*" It lists 640 manuscripts which are arranged in twelve classes

1 Grammatica (36 volumes), 2 Poetica (37), 3 Logica (27), 4 Rhetorica (12), 5 Mathematica (which includes Music, Astrology, Magic, and Necromancy 73 volumes), 6 Philosophia Naturalis, including Alchemy (64 volumes), 7 Metaphysics (15 volumes), 8 Philosophia Moralis (35 volumes including Sallust, Cassiodorus, Vegetius, Cicero), 9 Medicine (101 volumes), 10 Civil Law (7), 11 Canon Law (16), 12 Theology (213 volumes)

This library catalogue is not only remarkable for its extent and for its systematic arrangement, it even comprises the express mention of titles wanted "*quae volumina Dei adiutorio procurabuntur*" Amplonius also drew up the statutes and regulations for the use of his library Only post-graduate members of the Collegium Amplonianum had a right to be admitted, graduate members of other colleges had to apply to the Dean for admission Loans were permitted, but carefully regulated, and the library was to be open from eight to one o'clock Readers were admonished to be "*fideles in libris*"

The Bibliotheca Amploniana with its manuscript treasures still exists, and it numbers now 978 manuscripts having both suffered losses of its ancient stock and gained accessions in the course of the centuries It is a wonderful monument to a great man who was certainly one of the founders of scientific university studies in Germany, and a glory of the medical faculty of which he was a member

## LIBRARY NOTES

## BOOK REVIEW

Klebs, Arnold C *Incunabula scientifica et medica*, short title list from *Osiris* (vol 1) Reprinted

Bruges, The Saint Catherine Press, 1938 [iv], 359 p Issued as no 1 of the History of Medicine series under the auspices of The New York Academy of Medicine \$5 00

As stated in the introduction this work is offered primarily as a survey, "in the briefest possible terms", of the incunabula still extant on scientific and medical subjects As such, it is a model of conciseness, accuracy, and arrangement for future bibliographers As a pioneer in the field of subject bibliography for 15th century books, Dr Klebs had many things to determine, such as arrangement, inclusion of contents, and above all what to leave out so that his main purpose would stand out clearly The arrangement is by author, or, if anonymous, by a keyword Serial numbers are given only to the titles, of which there are some over 1,000 Editions are arranged under the titles, each given the title number followed by a decimal point and number, as 115 1, 115 2 for editions one and two of title 115, there are some 3,000 editions in all If an edition contains more than the main title would imply, the contents are fully listed following the entry, an added entry, in its proper alphabetical place, is made for each item, as listed, of the contents The contents and added entries are in a smaller type and are readily distinguished from the main entries

The work is preceded by a good seven-page list of bibliographical references arranged according to the abbreviation used for each of them Fifteenth century authors are noted, generally speaking, for the variety of forms under which their name has appeared in bibliographies Dr Klebs has wisely kept the

variant forms of such names from encumbering the main list by adding at the end of the book a seventeen-page list of "Cross References", referring from variant forms of an author's name to the one which he has chosen to use Dr Klebs has quite uniformly used the vernacular form of the name while some would prefer to use the Latin form, especially when the author's writings were entirely, or largely in Latin

The subjects include science and medicine in the broadest sense Some 800 editions are miscellaneous works, of which nearly one-half are prognostications and "practica", medicine, the largest class, has 850 editions, natural philosophy (botany, zoology, etc) 400 editions technology, with arithmetical, alchemical, agricultural, architectural, and musical tendencies, some 300 editions, astronomy, and of course astrology, some 200, and mathematics, including geometry, physics, etc, about 100 editions A good many would have liked to have seen the work arranged by subject, others would have liked to have had Dr Klebs include the valuable information which his knowledge and research must have had at hand, either, or both, of those arrangements would have detracted from Dr Klebs' objective a survey "in the briefest possible terms" It is hoped that Dr Klebs' information will become available, possibly in a new and enlarged edition by subject

Incunabula has probably received more attention from bibliographers than any other group or class of books, generally from the typographical approach with bibliographical descriptions Very seldom has it been attempted from the subject side, especially to include the whole output of a particular subject It is good to see one of Dr Klebs' ability contributing so much to subject bibliography through his researches Only

one who has worked considerably with this material can appreciate the immense amount of labor, research, and learning that has gone into this book, and the care that has been taken. Klebs 80815 *Prognosticationes*, 1494, and 808011 *Prognosticationes Practicae* (German) 1494, both imperfect, are apparently copies of the same edition and should be entered under Michael de Wratistavia, as the Huntington Library copy, also imperfect, fortunately has the leaf with title in which the author's name appears. Under Beroaldo, Filippo *Declamatio philosophi, medici, oratoris*, Hain 2961a may also be added as a 16th century imprint.

A few items in the Huntington Library may be suggested as additions to the work as follows: *Calendarium*, 1486-1504 Venice Leninger, 26 July 1486, a broadside *Epitaphides Anno Christi domini 1490* [Bale Kesler, 1489], *Kalendar, mit astrologischen bemerkungen*, Augsburg Balubier, 1481, a variant of Klebs 5691, *Sententiae uberioris ex scriptis Thomae et Alberti super Philosophia Aristotelis* [Leipzig, Kachelofen, about 1490, 1500], Urso, *De somniorum expositione* [Paris, Gering, about 1483] Versor, Johannes, *Questiones super metaphysicam Aristotelis cum textu* [Cologne Quentell, about 1493]

H R M

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## DEATHS OF FELLOWS

ABEL, JOHN JACOB Johns Hopkins University, Baltimore, Maryland, born in Cleveland, Ohio, May 19, 1857, died in Baltimore, Maryland, May 26, 1938 graduated in medicine from the University of Strassburg in 1888, received the degree of Doctor of Science from the University of Michigan in 1912, the University of Pittsburgh in 1915, Harvard University in 1925, and Yale University in 1927, the degree of Doctor of Laws from the University of Cambridge, England in 1920, elected an honorary Fellow of the Academy November 18, 1926

Dr Abel was professor emeritus of pharmacology at the Johns Hopkins University, having joined that institution in 1893 Prior to this, he was lecturer and professor of materia medica and therapeutics at the University of Michigan

He was a member of the Association of American Physicians, the American Physiological Society, Society for Pharmacology and Experimental Therapeutics, American Chemical Society, Honorary Member of the Philadelphia College of Pharmacy, and Fellow of the American Association for the Advancement of Science and its President in 1931

Dr Abel received the first award of the Lectureship of the Kober Foundation of the American Association of Physicians in 1925, the Willard Gibbs Medal of the Chicago Section of the American Chemical Society in 1926, and the gold medal from the Society of Apothecaries, London, in 1928

He was Editor of the Journal of Pharmacology and Experimental Therapeutics and contributed numerous works of research on animal tissues and fluids, and on the physiological and therapeutic action of various substances

BURLINGHAM, ROBERT 860 Park Avenue, New York City, born in New York City, February 29, 1888, died in New York City, May 28, 1938, graduated in medicine from the College of Physicians and Surgeons, Columbia University, in 1914, elected a Member of the Academy November 8, 1931 Dr Burlingham was a member of the American Medical Association and the State and County Medical Societies

CRIGLER, LEWIS WEBB 653 Park Avenue, New York City, born in Crawford, Mississippi, June 26, 1876, died in New York City, April 30, 1938, graduated in medicine from the Vanderbilt University School of Medicine, Nashville, in 1899, elected a Fellow of the Academy February 3, 1910

Dr Crigler was surgical director of the Manhattan Eye, Ear and Throat Hospital, ophthalmological surgeon to the New Rochelle Hospital and consulting ophthalmological surgeon to the Elizabeth A. Horton Memorial Hospital at Middletown and the United Hospital at Port Chester

He was a Fellow of the American Medical Association and a member of the American Academy of Ophthalmology and Otolaryngology and the State and County Medical Societies

HANSEN, EJNAR 2 East 54 Street, New York City, born August 23, 1870, died in New York City, May 13, 1938, graduated in medicine from the University of Maryland in 1904, elected a Fellow of the Academy February 5, 1914

Dr Hansen was a Fellow of the American Medical Association and a member of the State and County Medical Societies

HARVEY, THOMAS WILLIAM 59 Main Street, Orange, New Jersey, born in New York City, September 10, 1853, died in Orange, New Jersey, April 8, 1938, received the degree of Bachelor of Arts from Princeton College in 1875 and graduated in medicine from the College of Physicians and Surgeons in 1878, elected a Fellow April 1, 1897

Dr Harvey was consulting surgeon to the New Jersey Orthopedic and the Orange Memorial Hospitals

He was a Fellow of the American College of Surgeons, the American Medical Association, the American Climatological Society, the New Jersey Surgical Society and the County and State Medical Societies of New Jersey

HORN, JOHN 104 East 40 Street, New York City, born in New York City, September 7, 1856, died in Monterey, Massachusetts, June 11, 1938, graduated in medicine from New York University Medical College in 1885, elected a Fellow of the Academy May 2, 1901

Dr Horn was consulting surgeon of otology and rhinology to the Lenox Hill Hospital

He was a diplomate of the American Board of Otolaryngology, a Fellow of the American College of Surgeons, and a member of the American Laryngological, Rhinological and Otolological Society, the American Medical Association and the County and State Medical Societies

MABBOTT, JOHN MILTON 27 Washington Square, New York City born in Waterbury, Connecticut, July 14, 1862 died, July 1, 1938, graduated in medicine from the College of Physicians and Surgeons in 1884 elected a Fellow of the Academy March 1, 1894

Dr Mabbott was a member of the State and County Medical Societies, the American Medical Association, the New York Obstetrical Society, the Society of Alumni of St Luke's Hospital and Consulting Physician to the Northern Dispensary

PETERSON, FREDERICK, 555 Park Avenue, New York City, born in Feribault, Minnesota, March 1, 1859, died in New York City, July 9, 1938, graduated in medicine from the University of Buffalo Medical School in 1880, elected a Fellow of the Academy January 3, 1888

Dr Peterson was a member of the State and County Medical Societies, the American Medical Association, the American Psychiatric Society, the American Neurological Society, the New York Neurological Society, and the New York Psychiatric Society He was also Consulting Alienist to Bellevue, Central Islip and Manhattan State Hospitals, and Consulting Neurologist to the Neurological Institute and Craig Colony Hospital

STEDMAN, THOMAS LATHROP 1060 Amsterdam Avenue, New York City, born in Cincinnati, Ohio, October 11, 1853 died in New York City, May 26, 1938, received from Trinity College the degrees of Bachelor of Arts in 1874 and Master of Arts in 1896, graduated in medicine from the College of Physicians and Surgeons in 1877, elected a Fellow of the Academy May 6, 1880

Dr Stedman was surgeon to St Luke's Hospital from 1876 until 1879 and surgeon to the New York Orthopedic Hospital and Dispensary from 1881 until 1886 He was a Fellow of the American Medical Association and a member of the County and State Medical Societies

Dr Stedman was the author of a medical dictionary and a number of medical handbooks He was also the editor of many textbooks

## ANNOUNCEMENTS

### I STATED MEETINGS

The President and Council of the Academy, no less than the Committee on Medical Education, have long been concerned with the gradual decline of interest in the Stated Meetings on the part of the Academy membership. The program for the coming year is the issue of that concern, for it has been designed to provide meetings which no member desirous of keeping abreast of medical affairs can well afford to miss.

Even a cursory examination of this program will reveal the care exercised by the Program Committee in the selection of subjects of current interest and speakers qualified to present authoritatively the various aspects of these topics. A notable innovation for the coming year is the provision for consideration of controversial issues by invited commentators. In certain instances, discussion of the papers of the evening has been devised to invite conflicting opinions upon measures now before the medical profession.

The Committee has fixed as its objective, a program that will appeal to the Academy membership. The lack of interest recently manifested by the membership may be regarded as an indictment of this Committee, but the Committee feels that a lack of response by the Academy members to the evening programs for the Stated Meetings of 1938-39 will definitely be an indictment of the membership.

The complete program for these Stated Meetings follows. This notice refers only to the first Stated Meeting of each month. The program for the second Stated Meeting each month is arranged by the Harvey Society.

### PROGRAMS

October 6, 1938

#### *Evaluation of sulfamylamide therapy*

1. Fundamental problems of chemistry and pharmacology—mechanism of the action, E. K. Marshall, Jr., Baltimore

- 2 Clinical aspects, Reuben Ottenberg
- Discussion Emanuel Applebaum (Meningitis)  
Homer F. Swift (Rheumatic fever)  
William E. Studdiford (Gonorrheal condition postpartum infection)  
Francis G. Blake (Erysipelas)

December 1, 1938

*Serum therapy in pneumonia*

- 1 Present status of serum therapy, Russell L. Cecil
- 2 Results with rabbit serum, Colin M. MacLeod
- 3 Program for meeting the pneumonia situation, Wheelan D. Sutliff
- Discussion Edward Tolstoi  
Jesse G. M. Bullock  
Ralph S. Muckenfuss

January 5, 1939 — ANNUAL MEETING

*Chronic gastritis*

- 1 Recent advances in diagnosis by gastroscopy, Rudolf Schindler
- 2 Clinical aspects, Burrill B. Crohn

February 2, 1939

*Vitamins with special reference to therapy*

- 1 Vitamin A, Arthur M. Ludkin, New Haven
- 2 Vitamin B, Norman Jolliffe
- 3 Vitamin C, Gilbert Dalldorf, Vahlalla
- Discussion Arthur J. Patek, Jr.  
Soma Weiss, Boston  
Philip Finkle

March 2, 1939

*Symposium on arthritis*

- 1 Gout, Philip S. Hench, Rochester, Minnesota
- 2 The nature of hypertrophic arthritis (degenerative joint disease)  
Walter Bauer, Boston
- 3 Evaluation of newer methods of therapy, Ralph Boots
- Discussion Philip D. Wilson  
Edward F. Hartung  
Albert B. Ferguson

May 4, 1939

*Recent advances in the treatment of peripheral vascular disease*

- 1 Clinical manifestations, Irving S. Wright
- 2 Medical treatment, Edgar V. Allen, Rochester, Minnesota
- 3 Surgical treatment, Reginald H. Smithwick, Boston
- Discussion Beverly Chew Smith  
James C. White, Boston

## 2 THE ELEVENTH ANNUAL GRADUATE FORTNIGHT

*"Diseases of Blood and Blood-Forming Organs"*

OCTOBER 24 TO NOVEMBER 4, 1938

The attention of the Academy members is invited to the admirable program which has been arranged for the coming Graduate Fortnight by the Committee on Medical Education

The subject has definite interest for the physician and the surgeon and also includes phases which will interest specialists in each of these major fields

The Fortnight Committee merits the appreciation of the membership for the judgment manifested in the selection of speakers and topics, and for the excellent composition and integration of the program for the evening meetings

The Director of Clinics and the Hospital Committee, composed of representatives of eighteen hospitals in the Metropolitan area, have arranged for afternoon clinics, thereby providing for clinical demonstrations of every phase of the general subject

The response already received by the Director of Exhibits gives promise of an exhibit which will equal the really remarkable one assembled last year

The Committee is receiving so many requests for programs from all parts of the United States that it is apparent that the Fortnight has become an event of interest to the medical profession of the entire country. The Academy quite naturally welcomes the widespread interest in this undertaking, the purpose of which is essentially the dissemination of knowledge of advances in medical practice. The Officers of the Academy, however, particularly desire in this significant project the interest and sympathy of its membership

## PROGRAM OF EVENING SESSIONS

October 24, 1938

*Macrocytic anemias*

- 1 General aspects of the etiology, diagnosis and treatment, George R. Minot
- 2 Macrocytic anemia of sprue and allied conditions, C. P. Rhoads
- 3 Neural manifestations and their treatment, Maurice B. Strauss
- 4 Differential diagnosis and some observations concerning treatment, Cyrus C. Sturgis

October 25, 1938

*Anemias due to iron deficiency*

- 1 Etiology of iron deficiency, Clark W. Heath
- 2 Iron deficiency anemia in infancy, Louis K. Diamond
- 3 Iron deficiency anemia in pregnancy, Maurice B. Strauss
- 4 Concluding remarks on iron deficiency anemias, George R. Minot

October 26, 1938

*Refractory group of anemias and the granulocytopenias*

- 1 Aplastic and hemolytic anemias, C. P. Rhoads
- 2 The neutropenic diseases Roy R. Kricke

October 27, 1938

*Blood formation and destruction—hematohistology*

- 1 On the origin and developmental potentialities of blood cells, William Bloom
- 2 The reticulo-endothelial system, Harrison S. Martland

October 28, 1938

*Diagnostic procedures*

- 1 Diagnostic significance of changes in erythrocytes, Russell L. Haden
- 2 Diagnostic significance of changes in leucocytes, M. M. Wintrobe

October 31, 1938

*The leukemias and leukemoid states*

- 1 Infectious mononucleosis, John R. Paul
- 2 A clinical and pathological discussion of the common and unusual types of leukemia, Claude E. Forkner

November 1, 1938

*Malignant diseases of the lymph nodes and bone marrow*

- 1 Certain practical aspects of Hodgkin's disease and allied disorders, Henry Jackson, Jr.
- 2 The general pathology of lymphosarcoma, James Ewing

November 2, 1938

*The polycythemias*

- 1 Polycythemia, Paul Reznikoff
- 2 Diseases of the blood in infancy and childhood, Thomas B. Cooley

November 3, 1938

*The hemorrhagic diseases*

- 1 The Wesley M. Carpenter Lecture Hemophilia, William H. Howell
- 2 Classification and treatment of purpura, Nathan Rosenthal

November 4, 1938

*Diseases of the spleen and therapy*

- 1 The medical-surgical splenopathies
  - a Introduction, Allen O. Whipple
  - b Hemolytic jaundice, William P. Thompson
  - c Congestive splenomegaly, Louis M. Rousselot
  - d Thrombocytopenic purpura, Robert H. E. Elliott
- 2 Irradiation therapy in the blood diseases, Lloyd F. Craver
- 3 Concluding remarks, Charles F. Tenney

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BULLETIN OF  
THE NEW YORK ACADEMY  
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SEPTEMBER 1938

EXPERIMENTAL HYPERTENSION INDUCED  
BY RENAL ISCHEMIA

*Harvey Lecture, May 19, 1938*

HARRY GOLDBLATT\*

Professor of Experimental Pathology Western Reserve University

ALTHOUGH the direct method for the determination of blood pressure in animals dates back to Stephen Hales,<sup>1</sup> in 1733, and although the existence of a state of increased vascular tension in man was surmised on the basis of indirect methods, especially palpation of the pulse,<sup>2</sup> pulse tracings<sup>3-5</sup> and other bloodless indirect methods,<sup>6-8</sup> yet it was not until the development by Riva-Rocci<sup>9</sup> of the method of taking blood pressure (actually bursting tension) by the pneumatic cuff and mercury manometer that the existence and significance of human hypertension were fully recognized and the serious study of its cause was undertaken.

Whether or not disease of the kidneys plays a primary part in the pathogenesis of increased arterial tension has been the subject of speculation and controversy for a long time. More than 100 years ago, before blood pressure had been determined in man, Richard Bright<sup>10-11</sup> observed the frequent coexistence of renal disease of various kinds and hypertrophy

\*These studies were supported by the Beaumont Richman Kohn Fund and by special grants in aid from the Josiah Macy, Jr. Foundation, American Medical Association, Mr. Nathan Daub, and Mr. Alex. Wintner and associates of Cleveland.

of the heart for which he found no obvious cause in the heart or large blood vessels. He attributed the cardiac hypertrophy to an effect produced on the heart (increased action) or blood vessels (increased peripheral resistance) by an altered state of the blood which, he felt convinced, was caused by the renal disease, although he admitted the possibility that the renal disease might be the result of the altered state of the blood. Thus, although Bright knew nothing about hypertension, we now realize that he was the first to consider the possible renal origin of this condition. He tried to perfuse nodular kidneys and mentioned the resistance which the nodules offered to injection. Toynbee<sup>12</sup> found that this difficulty was due to thickening of wall and narrowing of lumen of the smaller intrarenal arteries. This has since been fully confirmed by direct<sup>13 16</sup> and indirect<sup>17 19</sup> methods. Johnson<sup>20</sup> showed that in such cases similar thickening in the small arteries was present in other organs, yet he offered the theory that the primary disease was within the kidney, and that cardiac hypertrophy and increased arterial tension were due to generalized constriction of the peripheral branches of the arterial system. For the vasoconstriction he had a far-fetched teleological explanation to the effect that the vascular disease would interfere with the passage of accumulated noxious substances from the blood into the tissues. Traube<sup>2</sup> was the first to express the definite view of a primary causative relationship between renal disease and increased arterial tension. This was based on the mechanical theory of the resistance which the disease in the kidneys offers to the loss of water from the blood and also to the amount of blood leaving the aorta, with consequent hydremia and increased arterial tension. This view has not been substantiated by subsequent authors except those who have used his theory as a basis for a teleological explanation of hypertension. It was principally as a result of the anatomical studies of Gull and Sutton,<sup>21</sup> who demonstrated the rather widespread distribution of organic disease of the smallest branches of arteries and the capillaries, which they called arteriocapillary fibrosis, that these generalized organic changes were seriously considered as the primary cause of increased peripheral resistance, with consequent hypertension and cardiac hypertrophy. The clear differentiation of chronic glomerulonephritis and renal arteriolar sclerosis<sup>22 23</sup> finally led to the recognition of Frank's<sup>24</sup> essential hypertension. The hypertension associated with chronic glomerulonephritis was quite generally regarded as renal in origin so that the problem became limited to the pathogenesis

of essential hypertension. To the followers<sup>25 26</sup> of Gull and Sutton, the cause of the hypertension appeared to have been explained, but there remained the problem of the cause of the primary vascular disease. The pendulum swung when it was realized that the organic disease of the arterioles, even in the most severe cases, was not sufficiently widespread to account for the increased peripheral resistance that is required to cause persistent hypertension. Huchard<sup>27</sup> and Allbutt<sup>28</sup> projected the idea that the hypertension, due to generalized vasoconstriction, is the primary manifestation and the organic vascular disease a consequence of this condition. Mueller<sup>29</sup> went so far as to assert that prolonged vasoconstriction in a localized zone, such as the splanchnic, could be the cause of essential hypertension. The problem then became one of finding the cause of such generalized or localized vasoconstriction, with the kidney not seriously considered as the primary source of this effect. Both groups considered the vascular disease of the kidney simply a part of the generalized disease process and did not assign to it a primary part in the origin of this type of hypertension.

It is now generally accepted that hypertension may be of renal origin but this is usually assigned to the hypertension that accompanies obstructive disease of the urinary passages, chronic glomerulonephritis, polycystic kidney, renal panarteritis and severe renal amyloidosis.<sup>30</sup> Yet there are those, like Kylin,<sup>31 32</sup> who go so far as to deny the renal origin of hypertension under all conditions and who regard the various types of renal disease accompanying hypertension as secondary or merely coincidental. Fishberg<sup>30</sup> has defined essential hypertension as persistently elevated blood pressure without known cause which, on neither clinical nor anatomical grounds, can be considered due to inflammatory or obstructive renal disease. Although Fishberg includes various types of hypertension in this category, yet by far the commonest is the type associated with so-called diffuse vascular disease. Most of the recent writers<sup>36 40</sup> on the subject have assigned this term to this condition and agree with Fishberg that it is not of renal origin. The usual arguments against the renal origin of essential hypertension have been (a) the frequent discovery of elevated blood pressure before there are any recognizable signs of impairment of renal function,<sup>42</sup> (b) the fact that in a large percentage of these cases renal insufficiency never does become manifest, and (c) the failure to find any anatomical signs of renal disease in some of these cases. Fishberg,<sup>33</sup> Bell and Clawson,<sup>34</sup> and Moritz

and Oldt<sup>35</sup> have found that at autopsy there is organic arteriolar disease in the kidneys of most individuals who have had essential hypertension, without signs of renal functional damage during life. Yet only Moritz and Oldt,<sup>35</sup> the most recent investigators of this phase, have drawn the conclusion from their results that the vascular disease of the kidney must be seriously considered as playing a primary part in the pathogenesis of essential hypertension. In the reports of cases of essential hypertension in which no intrarenal arteriolar disease was found,<sup>30</sup> the possibility was not usually excluded that severe sclerosis in some portion of the main renal arteries might have been the cause of renal ischemia. During the past year, in a few cases of hypertension without renal arteriosclerosis, severe sclerosis and narrowing of the orifice or lumen of the main renal arteries or the lumen of the larger extrarenal branches, obviously sufficient to cause renal ischemia, have been observed.<sup>41</sup> Formerly lesions of this kind have probably been overlooked and the cases classified as essential hypertension without renal vascular disease.

Experimental evidence or proof for the view that the kidney may play a primary part in the development of hypertension has been sought in a variety of ways that appear in the following summary:

#### A SUMMARY OF OTHER EXPERIMENTS DESIGNED TO DETERMINE THE POSSIBLE RENAL ORIGIN OF HYPERTENSION

##### *Bilateral nephrectomy*

- Mosler<sup>43</sup> (1912) Used rabbits. Insignificant elevation of blood pressure.
- Backmann<sup>44</sup> (1916) Used cats. No elevation of blood pressure.
- Cash<sup>45</sup> (1926) Used dogs. No elevation of blood pressure.
- Hartwich<sup>46, 47</sup> (1930) Used dogs. No elevation of blood pressure.
- Harrison, Blalock and Mason<sup>139</sup> (1929, 1936) Used dogs. No elevation of blood pressure in 16 out of 18 dogs.

##### *Reduction of the amount of functioning renal tissue*

- Grawitz and Israel<sup>49</sup> (1879) Used rabbits. Slight hypertrophy of heart, interpreted by the authors as due to hypertension.
- Passler and Heinke<sup>50</sup> (1905) Used dogs. Slight elevation of blood pressure.
- Backmann<sup>44</sup> (1916) Used cats. Slight elevation of blood pressure.
- Allen and collaborators<sup>51</sup> (1925) Used dogs. Slight temporary elevation of blood pressure.
- Mark<sup>52a, b</sup> (1925, 1928) Used dogs. Slight elevation of blood pressure.
- Anderson<sup>54</sup> (1926) Used rabbits. No elevation of blood pressure.
- Hartwich<sup>46, 47</sup> (1929, 1930) Used dogs. No elevation of blood pressure.
- Friedmann and Wachsmuth<sup>55</sup> (1930) Used dogs. No elevation of blood pressure.
- Chanutin and Ferris<sup>56</sup> (1932) Used rats. Great elevation of blood pressure.
- Wood and Ethridge<sup>86</sup> (1933) Used rats. Hypertension.
- Rytand and Dock<sup>57</sup> (1935) Used rats. Great elevation of blood pressure.

*Reduction of amount of renal substance by coagulation necrosis due to ligation of branches of renal arteries*

Janev<sup>58 59</sup> (1908, 1913), assisted by Carrel<sup>53</sup> (1909) Used dogs Slight elevation of blood pressure

Mark<sup>52b</sup> (1928) Used dogs No elevation of blood pressure

Hartwich<sup>46 47</sup> (1929, 1930) Moderate elevation of blood pressure Not persistent

Friedmann and Wachsmuth<sup>55</sup> (1930) Moderate elevation of blood pressure Not persistent

*Reduction of amount of renal substance by partial renal excision and unilateral nephrectomy combined with coagulation necrosis of part of the remaining kidney by ligation of branches of renal artery*

Cash<sup>60</sup> (1924) Used dogs Slight to moderate temporary elevation of blood pressure

Hantschmann<sup>69</sup> (1931) Used dogs Slight elevation Not persistent

Mark and Giesendorfer<sup>61</sup> (1930) Used dogs Moderate temporary elevation of blood pressure

Ferris and Hynes<sup>62</sup> (1931) Used dogs Slight temporary elevation of blood pressure

*Destruction of renal substance by irradiation of kidneys with roentgen rays*

Hartman, Bolliger and Doub<sup>63</sup> (1926) Used dogs Moderate elevation of blood pressure

Page<sup>89</sup> (1935) Used dogs Moderate elevation of blood pressure

*Renal infarction due to multiple emboli*

Senator<sup>65</sup> (1911) Used cats Injected liquid paraffin into renal arteries No rise of blood pressure

Cash<sup>60</sup> (1924) Used dogs Injected insoluble Berlin blue No elevation of blood pressure

Apfelbach and Jensen<sup>66</sup> (1931) Used dogs Injected particles of charcoal into renal arteries No elevation of blood pressure

*Occlusion of one main renal artery*

Hartwich<sup>46 47</sup> (1929, 1930) Used dogs Slight temporary elevation of blood pressure

Friedmann and Wachsmuth<sup>55</sup> (1930) Used dogs Slight temporary elevation of blood pressure

*Occlusion of both main renal arteries*

Katzenstein<sup>67</sup> (1905) Used rabbits and dogs No rise of blood pressure

Cash<sup>45</sup> (1926) Used dogs Moderate to severe elevation of blood pressure

*Occlusion (permanent or intermittent) of renal arteries, veins and ureters*

Cash<sup>45</sup> (1926) Permanent occlusion Used dogs No elevation of blood pressure

Loesch<sup>68</sup> (1933) Intermittent brief occlusion, every two or three days Used dogs Moderate persistent elevation of blood pressure

*Partial constriction of renal arteries (acute experiments)*

Katzenstein<sup>67</sup> (1905) Used dogs Very slight elevation of blood pressure

Bridgman, E W and Hirose, K<sup>74</sup> (1918) Used dogs No elevation of blood pressure

*Passive hyperemia (constriction of renal vein) of one kidney*

- Pedersen<sup>64</sup> (1927) and Bell and Pedersen<sup>70</sup> (1930) Used dogs Moderate temporary elevation of blood pressure  
 Menendez<sup>71</sup> (1933) Used dogs Slight temporary elevation of blood pressure in some, none in others

*Compression of kidneys by oncometer*

- Alwens<sup>72</sup> (1909) Used cats Acute experiments Slight elevation of blood pressure

*Permanent obstruction of ureters*

- Hartwich<sup>46, 47</sup> (1929, 1930) Used dogs Moderate elevation of blood pressure  
 Harrison, Mason, Resnik and Raine<sup>73</sup> (1936) Used dogs Moderate elevation of blood pressure

*Temporary obstruction of one ureter followed by release of obstruction and excision of other kidney*

- Rautenberg<sup>75</sup> (1910) Used rabbits Moderate elevation of blood pressure

*Effect of nephrotoxic substances*

- Dominguez<sup>76</sup> (1928) Used rabbits Injected uranium salts No elevation of blood pressure except in one animal that developed severe arterial and arteriolar sclerosis, especially in the kidneys  
 Arnott and Kellar<sup>77, 78</sup> (1935, 1936) Used rabbits Injected sodium oxalate Moderate temporary elevation of blood pressure  
 Scarff and McGeorge<sup>79</sup> (1937) Used rabbits Injected sodium oxalate No elevation of blood pressure

In some of the earlier investigations mentioned in the summary the hypertension that was observed was usually slight and lasted from only a few hours to several days. Some of the later investigators reported the development of hypertension of moderate degree and of short duration while others succeeded in producing moderate or severe hypertension of longer duration. Under practically every heading contradictory reports occur. Some of these experiments merely proved what is generally accepted, even for man, namely, the renal origin of hypertension associated with obstruction of the urinary passages or great destruction of renal parenchyma.<sup>30</sup> The contradictory results obtained by different investigators were due partly to the various methods, some indirect, like cardiac hypertrophy, which were used for determining the existence of hypertension, the different types of animal employed and the slight changes of blood pressure which were regarded as significant by some and not by others. For some of the contradictory results<sup>77, 78, 79</sup> there is no obvious explanation. The results of the experiments performed up to

1928 did indicate that various pathological changes in the kidneys could in some way play a primary part in initiating a degree of at least temporary hypertension in animals. By none of these methods was the condition produced in the kidneys comparable to that of the kidneys in human essential hypertension associated with arteriolar disease. It would appear that those experiments that were designed to prove the renal origin of essential hypertension failed for several reasons: 1. They were acute experiments and yielded negative or contradictory results in the hands of different investigators using the same methods. 2. In most of the chronic experiments, the experimental conditions did not reproduce or even simulate the anatomical or functional state of the kidneys in benign essential hypertension. 3. Hypertension, when produced, did not persist. Any method for the experimental determination of the possible primary part played by renal arteriosclerosis in the origin of essential hypertension should involve the production of at least the physiological effect of the renal vascular disease. It is not actually known, but it is at least probable, that the effect is a decrease of the flow of blood to the functioning elements of the kidney and a decrease in the intraglomerular capillary pressure. The latter would not be correct if the view is valid that there is spasm of the efferent arterioles<sup>80</sup> or the capillaries<sup>81</sup> of the glomeruli in essential hypertension.

Up to 1928, when the experimental investigations of the author were begun, no one had succeeded in producing either generalized arteriolar sclerosis or arteriolar sclerosis limited to the kidneys. For these investigations, therefore, the following working hypothesis was adopted: If organic disease of the kidney be the initiating factor in the pathogenesis of benign essential hypertension, then this disease is, in all probability, the arteriolar sclerosis which is so frequently associated with this condition. If arteriolar sclerosis limited to the kidneys can be the primary factor in initiating this type of hypertension, then the necessary conditions for the establishment of the renal origin of essential hypertension upon an experimental basis should be the production of hypertension in animals by any method which will produce at least the physiological effects of such renal vascular disease. Since there is no known way of producing arteriolar sclerosis localized to the kidney, it was thought that the effects of arteriolar disease could probably be produced by constricting the main renal arteries. Katzenstein,<sup>67</sup> and Bridgman and Hirose<sup>74</sup> did try to produce hypertension by constricting the main renal arteries, but the experi-

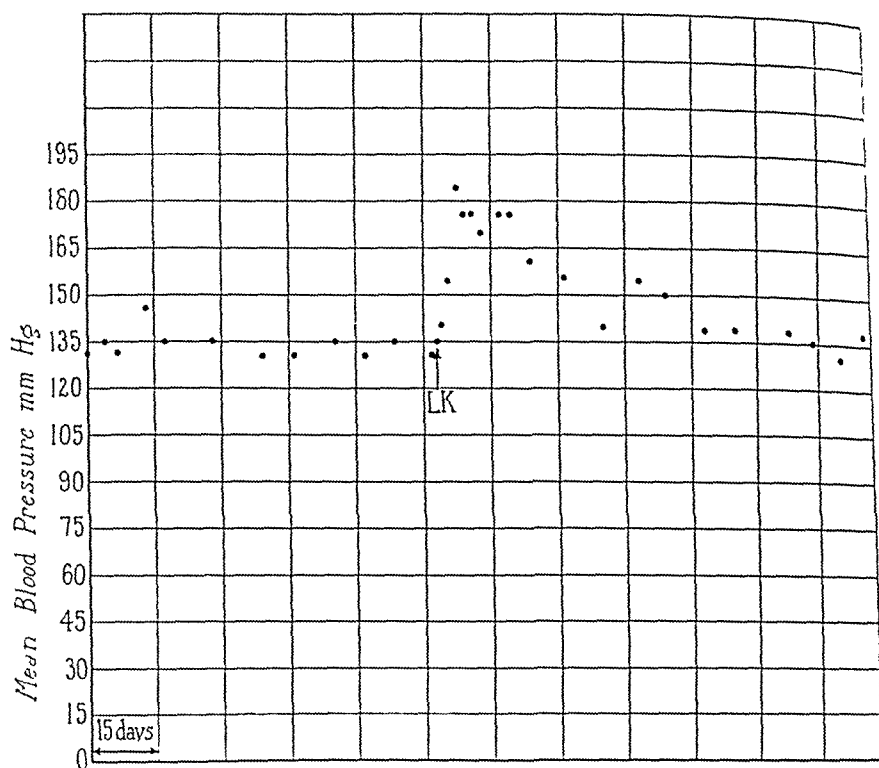


Fig 1—Dog-3-35, male, chow, young Initial weight 124 kg Final weight 140 kg LK = left main renal artery—moderately constricted ● = Mean blood pressure, mm Hg, direct method, femoral artery

ments were very short and their results contradictory Bridgman and Hirose observed no elevation and Katzenstein a very slight rise (10 mm Hg) of mean blood pressure For the purpose of the author's experiments, a special type of silver clamp was devised<sup>83</sup> whereby the main renal arteries could be constricted and their lumina reduced to any desired caliber It was first demonstrated<sup>83</sup> that decrease of the lumen of the main renal artery by varying degrees of compression caused an immediate corresponding decrease of blood flow through the kidney. Whether the decreased blood flow persists after hypertension develops has not yet been determined A decrease of intraglomerular capillary pressure as a result of this procedure has been assumed but not proved

In a series of experiments, by the use of this method, it has been found that, in the dog<sup>82 83 84</sup> and monkey,<sup>85</sup> constriction of the main artery of one kidney results in elevation of blood pressure which persists from weeks to months but usually returns to a lower or to the original level within one month (Fig 1) The adequate constriction of both

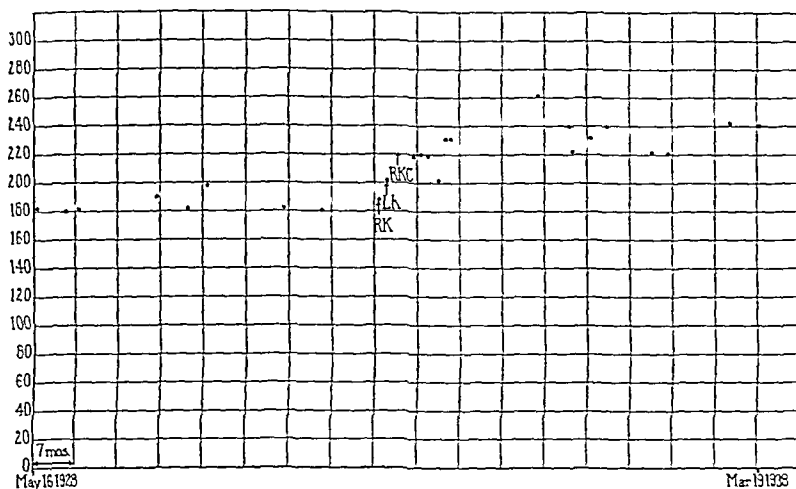


Fig 2—"Blackie", short-haired mongrel, female, age about 1 year, in 1928 Initial weight 21.4 kg Present weight 21.6 kg RK = moderate constriction of right main renal artery LK = moderate constriction of left main renal artery RKC = occlusion of right main renal artery The animal is still alive ● = Systolic blood pressure, mm Hg, van Leersum carotid loop method

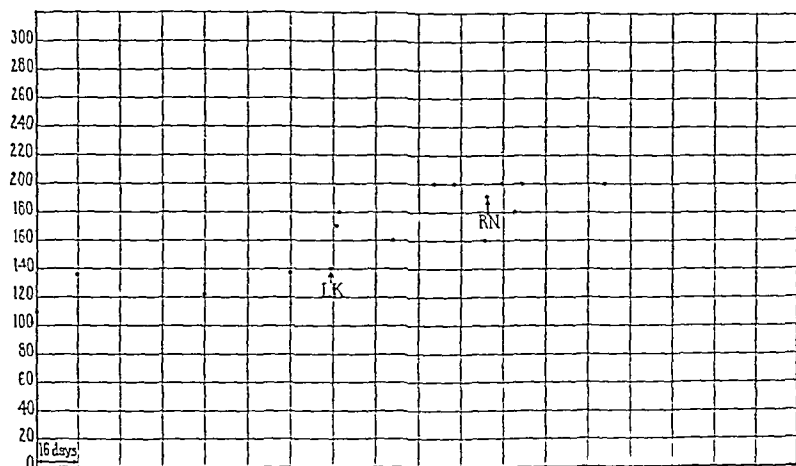


Fig 3—Dog 3-14, male, bull-dog, young Initial weight 11 kg Present weight 11.8 kg LK = severe constriction of left main renal artery RN = right nephrectomy ● = Mean blood pressure, mm Hg, direct method, femoral artery

main renal arteries at the same time, or with an interval between the clampings, results in persistent hypertension (Fig 2) The same persistent effect on blood pressure has been obtained by first constricting the main artery of one kidney and later removing the other kidney (Fig 3) In

some animals with both renal arteries constricted, the elevated blood pressure also tends after a while to return to a lower level. This is probably due to the development of significant accessory circulation to the kidney, which is naturally abundant in the dog.<sup>210</sup> In such dogs, increasing the constriction of the main renal arteries usually results in re-elevation of blood pressure. In some dogs, collateral circulation has become so well established that one or both main renal arteries have been finally entirely occluded and such animals have survived several years with greatly elevated blood pressure without accompanying significant impairment of renal function. It has been shown that the hypertension which has been produced by these methods in dogs and monkeys involves elevation of both diastolic and systolic pressure.<sup>84 85 91</sup> A similar effect in the upper part of the body can be obtained by constricting the aorta immediately above the origin of both main renal arteries.<sup>87</sup> Indirect confirmation of this is the development of left ventricular hypertrophy in the rat after constriction of the aorta immediately above the origin of the renal arteries.<sup>225</sup> Constriction of femoral or splenic arteries,<sup>46 47 48 83</sup> of splanchnic arteries,<sup>213</sup> or the aorta immediately below the origin of both renal arteries<sup>87</sup> does not elevate blood pressure. Most of these results have now been fully confirmed and amplified by many investigators.<sup>89 92,97,214</sup>

When the constriction of both main renal arteries, the main artery of the only kidney, or the aorta above the origin of the renal arteries is made moderate, there is no accompanying disturbance of renal function, detectable by the usual studies of urine and blood, including urea and creatinine clearance tests.<sup>83,84 85</sup> In some of the animals, with the main renal arteries constricted, the hypertension has persisted at a very high level for more than five years (Fig. 2). In the animals with the aorta constricted above the origin of both main renal arteries there has been a much greater tendency to return to the original level. In these, in order to make the hypertension persist, it has been found necessary also to constrict the aorta below the renal arteries. Despite this additional procedure, the accessory circulation to the kidney appears to be adequate to interfere with persistence of the hypertension at a high level.<sup>87</sup> In those animals that have had long standing hypertension, without accompanying damage of renal function, the only significant changes in the vascular system observed so far have been degenerative changes, mainly intimal, in the arterioles of the retina<sup>93</sup> and thickening of the media of the arterioles.

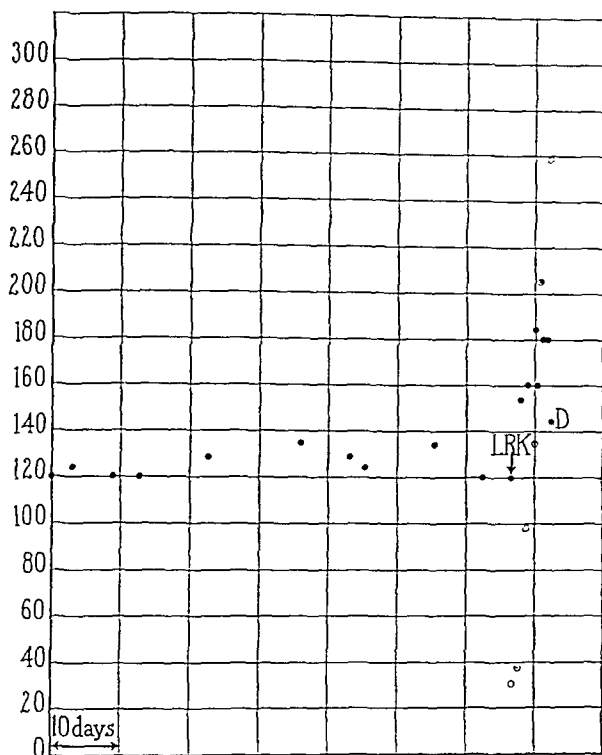


Fig 4—Dog 3-90, female, mixture of collie and airdale, middle-aged Initial weight 10.9 kg, final weight 12.2 kg LRK = almost complete constriction of left and right main renal arteries D = died ● = Mean blood pressure, mm Hg, direct method, femoral artery ○ = Blood urea nitrogen, mg per 100 cc of plasma

in other organs, especially skeletal muscle. The changes in the kidneys affect mainly the tubules. The organ may show but little change<sup>89</sup> or may undergo atrophy, depending upon the severity of the constriction.<sup>83, 84</sup> In such animals hypertrophy of the heart has been reported.<sup>82, 99</sup>

If the constriction of the renal arteries or of the aorta is made severe or complete from the beginning, disturbance of renal function usually accompanies the elevated blood pressure and the animal may develop fatal uremia.<sup>83, 84, 85</sup> In some of these animals (Fig 4) there develop widespread fibrinoid and hyaline degeneration, and necrosis of arterioles, with petechiae in some organs, similar in all respects to the lesions observed in the acute malignant phase of essential hypertension in man (see Plate).

The mechanism of development of the benign phase of experimental

hypertension induced by renal ischemia has now been the subject of extensive investigation. In considering the pathogenesis of this type of hypertension it has been assumed, for the same reasons as for human essential hypertension,<sup>30, 94</sup> that the responsible mechanism is increased peripheral resistance. Since, in the experimental animals, this cannot be regarded as due to initial organic change in the peripheral portion of the entire vascular system, the problem narrows down to the cause of the functional increase of peripheral resistance which follows the constriction of the main renal arteries. The teleological explanation<sup>208</sup> of purposeful increase of peripheral resistance in order to elevate the pressure and improve the blood flow through the ischemic kidneys is not susceptible to proof. There are, therefore, but two known mechanisms whereby the generalized constriction of arterioles<sup>30</sup> and increased peripheral resistance can be produced, namely, either a nervous reflex from the ischemic kidneys, which affects the general vasomotor apparatus, or a humoral mechanism initiated by the ischemic kidneys due to the formation or accumulation in the blood of a substance which, directly or indirectly, constricts the peripheral vessels. The possibility that such a substance might act on capillaries<sup>96</sup> or by neutralizing a natural depressor substance must also be mentioned.

That the ischemic kidneys are in some way directly responsible for the development of the experimental hypertension has been shown by

#### EXPLANATION OF PLATE\*

*This Colored Plate Represents a Photomicrograph in color Prepared by the Separation Method*

Fig 1—Arteriole in submucosa of large intestine. Beginning subendothelial deposit of hyalin. Endothelium well preserved. Hematoxylin and eosin  $\times 265$

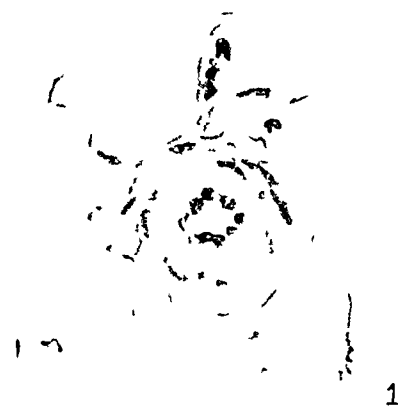
Fig 2—Arteriole in submucosa of stomach. Obliterative hyalinization of intima, endothelium still recognizable but nuclei reduced in number and pyknotic. Hematoxylin and eosin  $\times 430$

Fig 3—Arteriole in submucosa of small intestine. Lumen completely obliterated by accumulation of hyalin containing a few pyknotic nuclei. Hematoxylin and eosin  $\times 430$

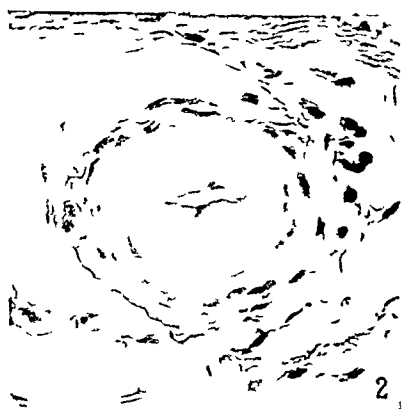
Fig 4—Arteriole in submucosa of stomach. Portion of entire thickness of wall necrotic. Normal thickness of wall and lumen natural size. Hematoxylin and eosin  $\times 325$

Fig 5—Arteriole, cut longitudinally, in submucosa and mucosa of large intestine. Partly hyalinized, partly necrotic, with extravasated blood around it. A portion of the same arteriole, in the submucosa, immediately proximal to the part included in this figure, was entirely normal. Hematoxylin and eosin  $\times 255$

\* This colored plate reprinted from the *Journal of Experimental Medicine* Vol 67 No 5, 1913



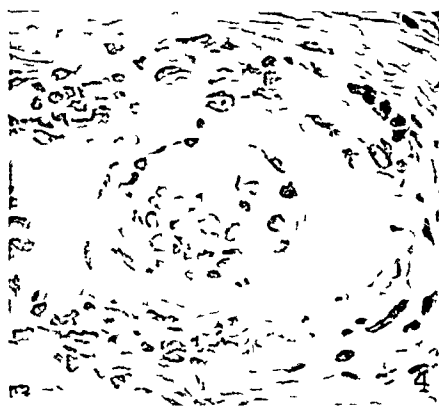
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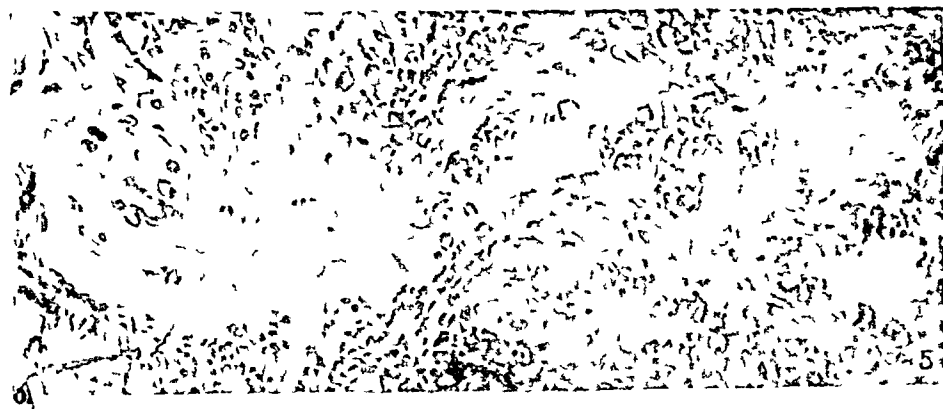
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the following experiments. If the main renal artery of one kidney is constricted and the ischemic kidney is removed some time later, when the blood pressure is still well elevated, the blood pressure falls promptly to the normal level.<sup>84</sup> If, instead of nephrectomy, the clamp on the one ischemic kidney is released or removed, the blood pressure also returns promptly to the original level.<sup>84</sup> If the elevated blood pressure is first produced by the constriction of the main renal arteries of both kidneys and only one clamp is released, the blood pressure falls slowly to the lower or to the original level in about the same time that it does when only one clamp is applied.<sup>84</sup> If, in a hypertensive animal, both clamps are released, the blood pressure falls promptly to the original normal level.<sup>84</sup> If one kidney is transplanted to the neck or inguinal region and the other kidney removed, constriction of the arterial blood supply to the transplanted kidney results in the development of elevated blood pressure.<sup>97, 98</sup> Bilateral nephrectomy is not followed by the development of persistent hypertension.<sup>43, 48, 84</sup> These results constitute evidence that the kidney is responsible for the effect and that it must be present in the body in order for the hypertension to occur.

The experiments that have been directed toward the study of the possible part played by a nervous reflex from the kidney have failed to establish this as the mechanism responsible for the increased peripheral resistance. In dogs, denervation of the renal pedicle<sup>89, 92, 99</sup> does not prevent or reduce hypertension due to constriction of the main renal arteries. This differentiates this type of hypertension from that due to intracisternal injection of kaolin<sup>105</sup> which can be prevented or reduced to normal by renal denervation. In the case of hypertension due to denervation of the carotid sinus and section of the depressor nerves the results of investigations of the effect of renal denervation have been contradictory.<sup>108</sup> Section of splanchnic nerves and excision of the lower four thoracic sympathetic ganglia,<sup>100</sup> section of the anterior nerve roots from the sixth dorsal to the second lumbar inclusive,<sup>101</sup> excision of the entire sympathetic nervous system in thorax and abdomen, including cardiac denervation,<sup>102, 104</sup> and even pithing,<sup>98</sup> have failed to prevent, or permanently to reduce hypertension produced by constriction of the main renal arteries. Finally, as mentioned above, if one kidney is removed and the other kidney is transplanted to the neck or to the inguinal region, and its main renal artery is constricted, elevated blood pressure develops.<sup>97, 98</sup> In such an animal there is no possible direct connection between

kidney and nervous system. The results of these studies eliminate a nervous reflex from the ischemic kidneys as the responsible mechanism for the initiation of the hypertension and leave only a humoral mechanism as the probable explanation of the phenomenon. These experiments do not eliminate the possibility that in human essential hypertension stimuli from the central nervous system may sometimes play a primary part and often an accessory part in elevating blood pressure above the level determined by the renal mechanism. It is probably the nervous factor which is influenced by the usual medical treatment of hypertension and accounts for any fall of blood pressure which results.

The failure of the various surgical procedures carried out on the nervous system to affect experimental hypertension due to constriction of the main renal arteries is probably due to the persistence of the effect on the kidney which cannot be materially altered by these procedures as long as the clamp remains applied. These experiments do not in any way controvert the results that have been obtained by the same procedures in the surgical treatment of hypertension in man.<sup>112 125 188</sup> They do emphasize, however, the importance of the renal factor as the primary cause of this type of experimental hypertension and probably of human essential hypertension that is associated with renal arteriolar disease. Since the renal factor in man is frequently due to narrowing of the lumen of only the arterioles of the kidney, without narrowing of the lumen of the large arteries, improvement of the circulation might result from the various surgical operations on the nervous system, as a result of relaxation of those arterioles in which the organic changes are not fixed. The lowering of blood pressure reported in about the same percentage of cases of hypertension by surgeons using various procedures which, directly or indirectly, affect the vasomotor nervous mechanism in the abdomen may, therefore, be due mainly to one cause, namely, the improvement of the circulation through the kidneys, and not, as has been suggested, directly to the relaxation of the arterioles in a large part of the vascular bed of the abdomen, independently of any effect on the kidneys. The latter view has no support in experimental observations.

All of the investigations that have been directed toward the study of the pathogenesis of this type of experimental hypertension have yielded results that indicate the existence of a humoral mechanism of renal origin that is responsible for the vascular constriction and consequent increased peripheral resistance which produces the elevation of the blood pressure

Removal of both kidneys does not result in elevated blood pressure, although the animal develops severe azotemia<sup>43 48 84</sup> On the contrary, sudden occlusion of the main renal artery of both kidneys, which also results in fatal uremia, does produce hypertension<sup>45 84</sup> Since occlusion of both main renal arteries does not eliminate all circulation to the dog's kidneys,<sup>210</sup> a chemical substance might still be washed from the kidney into the general circulation That this is most probably the case is shown by the failure of hypertension to develop when both main renal veins are occluded at the same time that the main renal arteries are constricted or occluded<sup>84</sup> This is due, presumably, to interference with the entrance of the hypothetical chemical substance into the blood stream If the ischemic kidney from one animal is transplanted to the neck of a nephrectomized animal, the blood pressure of the latter rises almost immediately after the circulation through the ischemic kidney is restored, while the transplantation of a normal kidney has no effect on the blood pressure<sup>126 127</sup> This has been interpreted as an indication that some chemical present in considerable concentration in the ischemic kidney, suddenly washed into the circulation of the recipient animal, produces an almost immediate pressor effect Whether such a "hypothetical effective substance"<sup>84</sup> actually exists and what its nature is has not yet been elucidated The normal kidney does not acquire this pressor substance in the short period during which it is without circulation before the transplantation is completed<sup>126 127</sup>

Since the original investigation by Tigerstedt and Bergmann,<sup>128</sup> who obtained a pressor effect with saline extract of normal rabbits' kidneys, when they injected it intravenously into other rabbits, many workers have repeated the experiments with different kinds of extracts, expressed juices and autolysates of normal kidneys of various animals, with conflicting results Some<sup>129 130</sup> confirmed Tigerstedt and Bergmann's finding, others<sup>131 133</sup> obtained only depressor effects, while most investigators<sup>134 138</sup> found both a depressor and pressor effect, the latter usually following the former Pressor effects have also been obtained with extracts from other organs<sup>142</sup> The search for the possible chemical substance involved in the humoral mechanism of renal origin in the cause of experimental hypertension due to constriction of renal arteries has resulted in a number of investigations that have dealt with the presence of a pressor principle in normal and ischemic kidneys Tigerstedt and Bergmann actually suggested<sup>128</sup> that there might be an increase

of the pressor substance, *rennin* they called it, in the kidneys of hypertensives. The recent isolation by Landis and collaborators<sup>224</sup> of an extract of normal kidney which elevates blood pressure without diminishing skin temperature and without reducing the amplitude of arterial pulsation is of special interest. A similar extract of ischemic kidney should be made and compared quantitatively with the extract of normal kidney.

Several investigators<sup>139 140 211</sup> have reported a larger amount of pressor substance in the watery extract of ischemic kidneys of experimental hypertension due to constriction of main renal arteries and of the arteriosclerotic kidneys of human hypertension as compared with that of normal kidneys. This does not constitute proof that this is the pressor principle involved in the production of hypertension which follows constriction of the main renal arteries or in essential hypertension in man.

Attempts to demonstrate a direct pressor substance in the systemic or renal venous blood or extract of the plasma of animals with experimental hypertension due to constriction of the main renal arteries have failed.<sup>143</sup> This differs from the result obtained with blood from animals with experimental hypertension due to the intracisternal injection of kaolin.<sup>209</sup> The results of tests made on the blood in human essential hypertension, both benign and malignant, have been contradictory, some obtained pressor effects<sup>144 172</sup> and others did not,<sup>173 184</sup> and the transfusion of blood in large quantity from a hypertensive individual to one with normal blood pressure had no effect on the blood pressure of the latter.<sup>185</sup> The pitfalls of investigations of this kind have been emphasized by O'Connor.<sup>186</sup> Thus there is no conclusive proof of the existence of a known or new pressor substance in the blood, spinal fluid, or urine in human essential hypertension, although it has been possible to obtain a pressor effect with blood from cases of paroxysmal hypertension associated with pheochromocytoma.<sup>226</sup>

The possible part played by the endocrine organs in the humoral mechanism of experimental hypertension due to renal ischemia has been the subject of investigation. Page and Sweet<sup>187</sup> have obtained contradictory results on the influence of hypophysectomy on this type of hypertension. Whereas the removal of the hypophysis had little or no influence in preventing this type of hypertension, yet hypophysectomy in hypertensive dogs was followed by a fall of blood pressure to a lower or normal level in some of the animals. The latter result may have been due to the development of adequate accessory circulation to the kidney.

and may not have been due to the effect of hypophysectomy. This investigation requires repetition.

The influence of the adrenals has also been studied.<sup>84</sup> The possibility of keeping bilaterally adrenalectomized dogs alive by means of substitution and supportive therapy<sup>189, 193</sup> has permitted the performance of a series of experiments on the effect of constricting the main renal arteries of such animals. Briefly, the results have shown that bilateral adrenalectomy without supportive or substitution therapy prevents the development of hypertension due to renal ischemia and causes previously produced hypertension to fall promptly to the normal or to a subnormal level. The result is the same even when supportive treatment in the form of sodium chloride and sodium bicarbonate or sodium citrate is given to the adrenalectomized animals. However, when presumptive substitution therapy in the form of cortical extract, as well as supportive treatment, is given, some of the animals do develop elevated blood pressure despite the absence of both adrenals. That it is the cortex and not the medulla of the adrenals that is important in this connection is shown by experiments in which one adrenal was completely removed, the medulla of the remaining adrenal destroyed, and the entire cortex<sup>83</sup> or only a small portion of it<sup>84</sup> left just sufficient to maintain life. In such animals, the blood pressure became elevated in the usual way when the main renal arteries were constricted. The results of many of the above experiments have already been confirmed<sup>97</sup> and Rogoff and collaborators<sup>227</sup> have shown recently that there is no increase of epinephrine secretion in this type of experimental hypertension. Just how the cortical hormone acts is not elucidated by these experiments. It may act only by playing its usual part in the physiological mechanisms and by insuring a normal state of the blood vessels of the animal. It may produce its effect by sensitizing the blood vessels to the action of the hypothetical effective substance of renal origin, or the reverse. The two substances may act synergistically. These are points that remain to be clarified. What these experiments do indicate is the futility of surgical<sup>194, 200, 227</sup> or other procedures designed to cure or lower hypertension in man by removal of one or destruction of portions of both adrenals, except in cases of paroxysmal hypertension associated with tumor of the adrenals.<sup>201, 207, 226</sup>

Nothing is known about the pathogenesis of the arteriolar degeneration and necrosis which are found in many internal organs, but most

frequently in the kidneys<sup>30</sup> and gastrointestinal tract,<sup>35</sup> in human benign or malignant hypertension. The degenerative and necrotizing arteriolar lesions of the animals which have been described above are not distinguishable from those found in most cases of malignant hypertension in man<sup>35</sup> except that they are more severe and more widespread than in the latter. This indicates a greater susceptibility of the dog's arterioles to these changes. In human malignant hypertension, skeletal muscles and lungs also rarely show necrosis of arterioles, although hyalinization and other changes may occur in those of the muscles.<sup>216</sup> The only striking difference between the lesions in man and dog is that in the latter the kidneys do not, while in the former they very frequently do show arteriolar necrosis. This discrepancy is easily explained and actually affords a clue to the pathogenesis of this lesion. In the animals, the intravascular pressure, within the kidney, is low, because the ischemia is due to the constriction of the main renal artery. In man, the intrarenal vascular tension is undoubtedly high, because there is sclerosis and constriction of the preglomerular arterioles. In some of the larger vessels of the human kidney the lumen is also frequently narrowed, due to proliferation of the intima, but it has never been shown that the arterioles belonging to such vessels become necrotic. It may be that only those arterioles become necrotic that are subjected to the high bursting tension as well as to the hypothetical toxic substance or substances in the blood which result from the renal insufficiency. There are some human cases in which necrosis of small renal arterioles is not found. These may be cases in which the renal insufficiency is due to widespread intimal proliferation in the small arteries and large arterioles and not to the reduction in the caliber of the preglomerular arterioles. This may also account for the difference and point to one of the probable factors and necessary conditions in the pathogenesis of arteriolar necrosis and hemorrhage, namely, elevated pressure within these vessels. That the accumulation of chemicals in the blood is not by itself a sufficient condition for the production of the arteriolar lesions, is shown by the fact that bilaterally nephrectomized dogs that develop azotemia but no hypertension<sup>84</sup> do not develop the generalized hyalinization and necrosis of arterioles and associated hemorrhages in the organs. That hypertension alone is not sufficient to determine the formation of the necrotizing lesions of the arterioles is shown by the fact that animals that have had severe hypertension for more than five years, without accompanying significant

disturbance of renal excretory function, have not developed this lesion. That the lesions of the arterioles are not due to ischemia is shown by the absence of the lesions from the severely ischemic kidneys of the dogs and their presence in organs in which there is no preexistent ischemia. In the dogs, at least, the combination of hypertension and severe disturbance of renal function, with consequent accumulation of chemical substances in the blood, is at least a necessary condition for the manifestation of the arteriolar necrosis and associated hemorrhages in various organs. Since the hypertension is not present within the intrarenal blood vessels of the animals with the main renal arteries, or the aorta above the origin of the renal arteries, constricted, the lesion does not manifest itself there. The same explanation (absence of local hypertension) probably applies to the absence of the lesion in the pulmonary arterioles of man as well as of animals. What the nature of the chemical substance or substances is that plays a part in the production of these lesions is not elucidated by these investigations on experimental hypertension that have been carried out so far but they do show that hypertension, severe disturbance of renal excretory function, and generalized degenerative changes including severe hyalinization and necrosis, of the arterioles, all indistinguishable from those found in the malignant phase of hypertension in man, can be induced experimentally by severe reduction of the blood supply to the kidneys.

The results of all the investigations that have dealt with the pathogenesis of the benign phase of experimental hypertension due to constriction of the main renal arteries apply equally well to the malignant phase. The only experimental condition that determines the type of hypertension is the degree of constriction of the main renal arteries.

One obvious surgical therapeutic procedure which suggests itself as the result of this work is the possible improvement of blood supply to the functioning components of the kidney by increasing the accessory circulation. In the animals with experimental hypertension induced by renal ischemia, whenever there is a return of the blood pressure to a lower level, it is due to inadequate initial clamping of the renal arteries or to the development of effective accessory circulation by way of ureteral and capsular vessels, which become very prominent. If, before constricting the renal artery, the kidney is decapsulated and adipose tissue or muscle is attached to the denuded cortical surface, the accessory circulation becomes very prominent and interferes with the development of

pronounced elevation of blood pressure. Since in the animals the constriction is only of the main renal artery, such accessory circulation can be of functional significance. The fact that animals have survived several years the complete closure of both main renal arteries,<sup>84</sup> when effected gradually by increasing the constriction at intervals, is proof that such accessory circulation can be functionally highly effective. Unfortunately, in human essential hypertension, the vascular disease most frequently involves also the preglomerular arterioles, so that collateral communication with the larger vessels would not improve circulation to glomeruli. Whether improvement of blood supply to some glomeruli, to tubules and interstitial tissue would occur and whether it would be effective in lowering blood pressure in human essential hypertension cannot be determined without trying. Although the author has hesitated to recommend it, yet there is probably more justification on an experimental basis for making this test than there has been for some of the surgical procedures that have already been practiced. The cases in which the production of accessory circulation would be most effective would be those in which the hypertension is due to sclerosis of the main renal arteries alone<sup>41</sup> or their very large branches. The difficulty of making such a diagnosis is obvious, so that unless the method could be applied to essential hypertension associated with renal arteriolar sclerosis the procedure would be of greatly restricted value.

An interesting practical application of this work, which centers upon the renal origin of so-called essential hypertension, has been the finding in children<sup>217</sup> and adults<sup>218</sup> of hypertension associated with unilateral pyelonephritis and vascular disease, and the prompt return of the blood pressure to normal after excision of the diseased kidney.<sup>217 218</sup> Until 1930, according to Bell and Pedersen<sup>219</sup> hypertension associated even with bilateral pyelonephritis had not been reported. Since then several authors<sup>220 223</sup> have reported this occurrence in some cases and from the meager studies of the kidneys in these cases it becomes probable that the hypertension associated with unilateral or bilateral pyelonephritis in children and adults occurs only in those cases in which there is associated vascular sclerosis or in which the inflammatory disease produces the same effects on renal circulation as does vascular disease. In cases of unilateral arteriolar nephrosclerosis with hypertension, which have been reported by Moritz and Oldt,<sup>35</sup> if the diagnosis could be made in life, removal of the diseased kidney might result in a return of the

blood pressure to normal, as in the cases of unilateral pyelonephritis.\* Unfortunately, unless the production of accessory circulation would be effective, nothing but transplantation of a normal kidney or kidneys, with removal of both diseased kidneys, could be expected to relieve the hypertension and prove the renal origin of the disease in cases of human hypertension associated with bilateral pyelonephritis or arteriolar sclerosis of the kidneys. Whether this can ever be accomplished in man as it can in animals, is for the future to disclose.

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\* From the James Buchanan Brady Urological Institute and Department of Medicine of Johns Hopkins Hospital there have just been reported<sup>22, 23</sup> two cases of hypertension associated with unilateral renal vascular disease in which the removal of the diseased kidney resulted in a prompt return of the blood pressure to normal. A similar result has been obtained in a third unreported case (Personal Communication Professor Hugh Young).

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## ENDOSCOPIC PROSTATIC RESECTION\*

JOSEPH FRANCIS MCCARTHY

THE title, Transurethral Resection, which seems to enjoy considerable usage, lacks precision and euphony and is a reversion to the era in medicine of resounding and ambiguous phraseology "Endoscopic Prostatic Resection" has none of these defects. The term implies the removal through the urethra, with an endoscope, by means of an electrically charged cutting loop, or a punch, or both, of serial sections of obstructing prostatic tissue, the objective being the restoration of the normal canular character of the prostatic urethra in exaggerated degree. This was the concept of the writer at the inception of this work and it remains unchanged. A number of highly qualified urologists, however, entertain the conviction that what amounts to subtotal prostatectomy is or should be the desired objective.

The mortality in endoscopic resection is, generally speaking, lower than in open prostatectomy. If trustworthy statistics are submitted indicating that the late symptomatic results are as good as those of open prostatectomy, we shall be quite willing to revise this opinion.

In this operation, one must of necessity give heed not only to the gland itself but to the contiguous structures as well. The physiology, pathology and bacteriology are, or should be, matters of concern.

There is, it appears, a too casual acceptance and a disproportionate stressing of the obstructing phase of prostatism. The patient knows he has an increasing hindrance to the normal act of emptying his bladder, that because of the frequency of this act, his night's rest is disturbed, that he has or has not pain, or disability. He wants relief or cure by the simplest, the safest, and the least time-consuming method. Above all, he does not want an open surgical operation. This is especially pertinent to doctors so afflicted. Here is the first prostatic problem of today and the urologist has now not only the question of selection of method of procedure, but in the event this decision is not in accord with the patient's

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esire for instrumental methods, a still more difficult problem

The whole subject of prostatism with its multi-faceted aspects, is topic of ever increasing interest Physical debility generally antedates mental senility, and because of the age range of these patients, we are dealing with a group who know their world and frequently are leaders in it If, as is probably the case, 25 per cent of all men experience this trouble—individuals at the peak of their mental capacity though perhaps well on the road of physical decline—the minimal contribution to this tremendously important problem, on the part of those who regard themselves leaders of thought in this field, is complete detachment from preconceptions, personal predilections, prejudices, and aptitude for a given method

My own experience with instrumental correction of established prostatism has been barometric, to say the least, moments of exaltation wherein the problem appeared to be completely solved Errors of interpretation, of judgment or of technique occurred, however, with sufficient frequency to bring about the salutary conviction of the desirability of moderation In a communication of several years ago, quoting from memory, I stated that endoscopic prostatic resection will not be fostered by unbridled enthusiasm, nor hindered by prejudiced neglect, that if it had intrinsic merit it would carry on of its own momentum If it did not have such merit, time would reveal this defect Now, some eight years later, the situation is somewhat as indicated in a recent communication in the *Journal of Urology* "It has been interesting to note the varying trends of the time In an increasing number of the larger clinics, a degree of enthusiasm is manifested for closed surgery, which at least equals that of the original proponents of these methods The conclusion to be drawn from this situation is, that while technical ability and judgment are vital, a fine organization is of equal importance Such at least is the deduction of the writer Individuals, it should be pointed out, or the occasional adventurer in this field of endeavor, cannot hope to achieve such results The other extreme of viewpoint is represented by a group of urologists of unquestioned ability, who relegate this type of surgery to a relatively minor rôle Paradoxical as this appears, both are right This last mentioned group have developed a high degree of skill in open surgery, results in their hands are better than with other methods Such individuals must elect to serve a more or less prolonged apprenticeship, a period fraught with travail, with a coincidental higher mortality, developing facility

with technical methods to which they may not be adaptable, either temperamentally or by past experience. One elects to do that which one does best, whether it be tight rope walking or steeple climbing. Prostatics will, perhaps, be all the better for the pursuit of this practice." As an elaboration of this question, it may be stated that there is a much larger group who employ the method in a considerable percentage of prostatics, who regard it as a preferential procedure in selected cases. While it is an invaluable addition to the urologist's equipment, it is still supplemental and does not replace the various and longer established open methods.

There are two prime objectives in endoscopic resection, first, the removal of sufficient encroaching prostatic tissue to effect complete restoration of function, and to minimize the likelihood of recurrence. Second, the avoidance of injury to adjacent parts. These structures are the verumontanum externally, the trigon internally, the seminal vesicle through its ejaculatory ducts, and the external sphincter. Any operator in this field should be mindful of the following fundamentals. First, as previously reported, that while on the floor of the internal sphincter, there is a very considerable margin of safety, immediately posterior to this point, the safety factor is greatly reduced. Indiscriminate digging at this point with an electrically charged loop, may easily result in sub-trigonal infection. It was for this reason that, in this part of the operation, we now employ the visualized punch instrument previously described in this journal. Injury to the veru may also be avoided by carefully adjusting the telescope so that the terminal of the sheath on the floor is within the visual field. This holds good for both punch and electrotome. Thus, one may observe precisely, the anterior limit of the cutting trajectory.

Considering the prostatic urethra as a circle, any experienced prostatectomist knows that the weakest part of that circle is its superior aspect. The technique of intra-urethral enucleation is based on this fact. One, therefore, should exercise the greatest caution in the removal of prostatic tissue, above ten and two on the clock. One personal experience of extravescical seepage as the result of too liberal tissue removal at this point, is the occasion for the suggestion. Moreover, one should have a precise appreciation of size and type of gland structure, by rectal palpation, immediately after the administration of the anesthetic and before the operation."

## PREOPERATIVE MANAGEMENT

Preoperative study of these cases is particularly exacting. We are dealing with elderly men. The cardiovascular system, therefore, must be minutely investigated. Electrocardiograms should be routine. Diabetics and hypertensives, if one is to follow the dictates of prudence, should have a preparatory period during which every effort should be made to bring such individuals to their peak of resistance to any operative experience. Hypertensives especially should, whenever possible, be guarded against violent blood pressure fluctuations, inasmuch as the added foot pound pressure at blood vessel terminals may, and not infrequently does, present difficulties in the adequate arrest of bleeding without undue coagulation.

## PREOPERATIVE INFECTIONS

I have never been able to subscribe to the commonly held belief that these patients are all the better for the presence of an infected urine, with its inevitable corollary, an infected prostate. If such theory ever had any merit in open prostatectomy, which I seriously doubt, how can it be supported where the operation is performed in a closed and highly permeable canal wall such as lines the prostatic urethra? I use No. 10 or 12F catheter decompression with a Drummond irrigator, and regulation of the hydrogen-ion content of the urine, which any intelligent nurse can report with the newer kinds of quantitative litmus and chlorophenol red, with colorimetric charts. With modern medication, the hydrogen-ion content of the urine can thus be regulated with almost test tube accuracy. This is a much more scientific form of management than the haphazard methods of the past. The precaution appears especially important inasmuch as most of the literature on this subject emphasizes infection as one of the major difficulties. Finally, the very badly infected, the hyperretentive types, may be all the better for a preliminary cystotomy. In effect, it consists of a transverse incision 5 cm. in extent, and about the same distance above the posterior aspect of the middle of the symphysis. Skin, subcutaneous fat and muscle sheath are thus incised, the muscle then bluntly separated in a longitudinal direction. The bladder, which has previously been partly filled, has an indwelling catheter with bulb syringe filled with metaphen solution. The underlying bladder is then palpated as it is further distended by this fluid. Sharp dissection then

exposes the organ which is also incised transversely. Advantages—there remains practically no space for drainage, the prevesical space is untouched and, as a consequence, absorption and infection are reduced to a minimum, hernia has never occurred and closure is effected on an average of twelve days, constitutional reaction is minimal, and finally, it has very materially reduced our operative mortality in open prostatectomy. The only reason that may be advanced for the customary longitudinal incision is precedent.

While it is true that endoscopic resection does not, as a rule, exert material effect on the nitrogen retention of the blood stream at all comparable to open prostatectomy, nevertheless, it is good practice to bring about a reduction of these elements to the patient's normal or pathological minimum. The foregoing methods are in conformity with the tenets of good medical practice, and any departure from these principles, fallacious.

#### CASE SELECTION

Until endoscopic resection by whatever method achieves general acceptance as a replacement for prostatectomy, it is the part of wisdom to segregate these cases carefully and to allocate the procedure to the type of prostate, rather than arbitrarily force all types, regardless of conformation or pathological status, down the chute of any one method. No single method is all inclusive. It may very well be that time and inevitable technical advance will bring about this highly desirable situation, a claim made by some writers at the moment. In this evolutionary period, however, we are justified in making haste slowly. It is still my belief that the obviously infected, the very large prostates involving of necessity prolonged operations with excessive coagulation, the mechanically difficult, the intravesical types and especially the subtrigonal extensions, may be and as a rule are all the better for open operation.

For some years, I have employed for prostatic resection, an instrument conceived by me, designed and constructed by Frederick Wappler, called the Visualized Electrotome. It has come into universal use. Here, as in any revolutionary surgical procedure, the method has experienced its period of trial and error. It has been essayed by many individuals without the necessary preparatory training and surgical background. In this connection, every one of my publications on this subject has carried a warning of its technical difficulties. Despite this, the devotees of the

od are being constantly augmented. In a considerable number of field clinical centers, it has practically replaced open prostatectomy now and always will be most exacting in its technical demands. I am convinced, however, despite the extreme enthusiasm manifested by a number of recent contributors, that obstructing prostaticitis merits a more judicious allocation of method to case, rather than case to method.

During these evolutionary years, it has been my constant endeavor to effect technical improvements, and to detect defects or deficiencies in technique. While this endoscopic vision is incomparably the best yet devised, and the illumination brilliant, the one weak point in its accomplishment is the operative removal at the floor of the vesical sphincter in the mid-line. Here, an unwary operator may inadvertently penetrate the peritoneum with the cautery loop. To obviate this defect we have adapted to the original Young punch, the panendoscopic telescope and a pistol grip.

At the moment, our present technique is to resect with this instrument the structures in proximity to the internal sphincter, using the cold punch, coagulate the bleeders with an electrode attachment, and complete the canalization as in a plastic operation, with the electric loop. If there be a single instrument or method sufficiently flexible to cope with the manifold aspects of obstructing prostaticitis, it is this so-called Visualized Electrotome. Nevertheless, our philosophy is that here we are dealing with a surgical entity, which can best be managed by a rational selection from diversified equipment.

### PUNCH METHOD

It is our belief that the punch instrument, hot or cold, has a logical application only at or about the vesical neck, that the cold punch is cold only in the actual excision and must be supplemented by cautery or electric coagulation in the arrest of hemorrhage, and that for the precise removal of intraurethral intrusions of prostate anterior to the above mentioned point, the electrotome loop is much to be preferred. It should not be inferred that in our hands, the punch instrument is routinely employed, even in the restricted field for which it was constructed, rather be it understood that, with a diversified equipment, the instrument most appropriate for the condition is the one selected, just as in any other surgical procedure.

## COMPLICATIONS

Before a navigator is assigned a post of considerable responsibility he must first experience fogs, storms, hurricanes and all the other vicissitudes incidental to the varying moods of the sea. So, too, must the qualified surgeon carry in his subconscious mind indelible impressions of trying and at times soul searching incidents in the course of his career, which enable him the better to meet similar emergencies which, from time to time, inevitably arise. Having experienced almost every complication associated with this particular field of surgery, I may therefore discuss with some authority the methods of their prevention.

## INFECTION

This may be divided into the acute urosepsis and the late postoperative pyurias. With the acute type, our experience is limited to a very few cases. This we attribute to the fact that our cutting current has been of the tube type and relatively superficial in its action. Our interpretation of the etiology in our own cases was an infected background, incomplete preliminary sterilization, and excessive instrumentation immediately post-operative. The spark gap current is employed by us only for purpose of coagulation. One cannot help but wonder if the excessive use of the spark gap current, both for cutting and coagulation, may not be a contributing cause in the types of infection mentioned.

It is my understanding that in the act of cutting with the gap machine, only a portion of the current does the cutting, the rest of the current acting as a coagulant. As a consequence, there occurs a greater degree of tissue destruction. Obviously, therefore, a relatively bloodless operation is not necessarily a good one. Then, too, nature must laboriously throw off every last particle of coagulated tissue before complete convalescence has been achieved. With the tube type, there is a better cutting action and a more superficial sealing. This seems logical for the reason that the pieces excised with the gap machine are cooked if not carbonized, whereas the pieces removed by the tube type machine are susceptible of histological examination. On the other hand, it seems that the gap machine is better for subsequent coagulation and when not overdone may be quite superficial in its action.

The late pyurias have been more frequently observed. Turbidity of the urine may be a matter of a few weeks, but infections may persist. Generally speaking, they are asymptomatic and a matter of more con-

cern to the doctor than to the patient. Two cases come to mind. In one, the infection was completely controlled while urotropin was administered, only to return when it was withdrawn. This condition has since cleared up under the treatment later outlined. The organisms in this case were paracolon bacilli and enterococci. In the other, an asymptomatic pyuria continued about three years during which time the patient was perfectly satisfied, but I was neither contented nor satisfied. The organism in this case was non-hemolytic *Staphylococcus albus*. There was no response to treatment of any sort until two months ago when prontosil was administered together with an iron preparation. Quantitative hydrogen-ion readings with nitrazine paper were made. There promptly ensued a spectacular clearance of the urine and the same improvement in the microscopic slide of the prostatovesicular secretion. This condition has been maintained, the prontosil having since been withdrawn. This treatment is now routine in all our resection cases.

Observers at Bellevue Hospital have noted that in the employment of prontosil, it is unwise to administer other medicaments, even such simple preparations as milk of magnesia or aspirin. Repeated hemoglobin and red cell estimations should also be scrupulously carried out, because of possible anemia attending its administration. It may also be well to avoid coal tar products because of the possible presence of the sulphur radicle.

#### INDICATIONS

Preliminary knowledge of the bacteriology of urine and prostatic secretion is necessary. Anticipate infection by preoperative sterilization where possible. Try the method above described in suitable cases manifesting protracted pyurias. At operation, employ punctate coagulation of isolated bleeders and compression bag for venous ooze. Do not leave behind a cooked deep urethra. Avoid unnecessary instrumentation.

Bleeding incidental to operation or immediately postoperative is, we believe, best controlled by the method previously described. This has been our chief difficulty. Particular care should be observed in coagulation of isolated bleeders at the vesical aspect of the sphincter. It is at this point that the compression bag is least effective. A return flow free from macroscopic blood should be routine. The Foley compression bag and catheter constitutes one of the really important technical advances in this field. Foley calls attention to an interesting step in technique. In effect he advises that whenever the compression is not wholly satisfac-

tory the bag should be rotated. The obvious reason for this step is that the pressure may be uneven. The closed aseptic irrigating system devised by Drummond, a former resident, is another forward step in the achievement of technical perfection. A necessary requisite in the employment of this system of drainage is that the caliber of the system, catheter, connecting glass, and rubber tubing be uniform throughout. After all, it is simply a plumbing system, but even a plumber's apprentice would laugh to scorn the drainage apparatus one sees. Finally, it is important that the resident accompany the patient from the operating room to the bed and immediately establish drainage.

Every urologist knows that clot retention is the greatest factor in postoperative oozing. As a consequence, much thought has been given this matter. We have employed every known type of clot aspirator from the long established bulb evacuator to electric pump aspiration under vision. We are gradually coming to the conclusion that the simpler and less expensive the evacuator, the more general will be its employment. In a few cases of annoying ooze, following the advice of Kretschmer, we have used hot solutions of 1-5000 silver nitrate with gratifying results. A wise precaution in bladder irrigation in this type of case is the avoidance of undue distention of the organ. Two or three fluid ounces should be the maximum at any one time.

Hemoglobin estimation and red cell count before and after operation, as suggested by Gilbert Thomas, will supply interesting data in both closed and open prostatic operations. Persistent oozing should not be too long tolerated. Procrastination is not a good hemostatic. An endoscope or electrotome should be introduced and a search made for the bleeding points which are coagulated. Failing in this, and we have so failed on a number of occasions, subordinate pride and cystotomize, as previously described.

### URETHRAL STRICTURE

The urethra of every patient should be calibrated before operation. It is a reasonable supposition that an occasional case may harbor a large caliber stricture (Ballenger's wise suggestion). Urethral stricture is undoubtedly an occasional complication, it is also an occasional complication of prostatectomy. It should be remembered that we are divulging an encumbered urethra over a protracted period. Prior to the advent of this procedure, no urologist would think of leaving a No. 28 sound

domiciled in a patient's urethra for any such period of time. How to prevent the rare case of stricture is our concern. I have come to the conclusion that a water soluble lubricant is inadequate for the purpose. It is too soluble and too easily absorbed. The back and forth manipulation of the dry sheath may therefore cause a desquamation of the epithelial lining of the urethra, a precipitating factor in stricture formation. It should be remembered also that water soluble lubricants are extremely good conductors of electric currents. Moreover, I am authoritatively informed that the addition of the usual lubricating media to water greatly increases this conductivity. It seems to me that the entire urethra should be lubricated with some type of oil media, taking care that it does not escape into the bladder where it will befog the lens. The flash point of all lubricants should also be borne in mind. The flash point in all the oils used as lubricant, however, is very high. Further, if the instrument be removed for whatever cause, the anterior urethra should again be lubricated. I entertain the thought that with such precautions and with minimal operative time, stricture as a complication should prove a negligible factor.

#### INCONTINENCE

At the moment of this writing, I cannot recall anything worse than an occasional case of temporary dribbling, which promptly cleared up. Of course, excessive coagulation or excision of tissue at the external sphincter may bring about such a condition. In an operation so precise as prostatic resection, this is an easily avoidable technical error.

#### PERMANENCY

This is largely dependent upon the thoroughness of the resection. In my experience, all functional requirements are met when complete canalization has been established. One should be at pains to remove all lobulated intrusions, especially in the superolateral portion of the canal. This need not, however, be carried to the point of subtotal prostatectomy. This position is in conformity with the contention so frequently made, that when the obstruction is relieved, there is a recession of the residual prostatic tissue. Moreover, when instrumental prostatectomy is practiced, there is a concomitant increase in the time involved, as also in the amount of coagulation. Then, too, there is left behind a minimal amount of prostatic tissue which should serve as a protective barrier to adjacent

structures and, finally, the patient has lost his prostate

Nor can I go along with those among my colleagues who so boldly attack sub-trigonal extensions of enlarged prostate with the electrically activated loop. The trigon is a triangular muscular platform which nature lays upon the bladder floor. When part of this structure is excised and infection ensues, a trigon thus infected may dissect itself away from the bladder wall proper, a very serious complication.

### MORTALITY

Analysis of statistical tables of recent publications presents some incongruities. With some exceptions, the lowest mortality figures are presented by operators who are essentially instrumenteurs. Much higher figures, though still low, considered in terms of prostatic mortality, are submitted by urologists who have performed a great many resections, and who because of their broad training, are capable of coping with any contingency. Another interesting observation in a statistical survey by Orr, D. T. and Rue, L. R., is the citation of 14,104 resection cases as against 5,062 prostatectomies. Again, as might be expected, where 100 or less resections were performed, the mortality rate is considerably higher than with operators who have performed 500 or more operations—the penalty of apprenticeship. In general, it may be said that resection mortality, in competent hands, will probably vary between one and four per cent inclusive, depending on the risks assumed, and in individuals ranging from fifty to ninety or more years. It should also be stated that there is a progressive lowering of death rate in open surgery. It is quite within the realm of probability that the statistics from two-stage suprapubic prostatectomy, wherein the transverse approach to the bladder is employed, will approximate the above figures. Perineal prostatectomy, as a matter of fact, has always been notable for its low mortality. It is to be doubted if appendectomy performed in this age range could present a better report. It also compares quite favorably with figures from the Bureau of Vital Statistics.

### PERTINENT FACTORS

Low mortality seems to me overemphasized in the publications coming to my attention. Morbidity, a very important feature, is discreetly overlooked. Late symptomatic results, while for the most part satisfactory, are not as good as in prostatectomy. This communication is a

departure from the customary publications on endoscopic resection, wherein, as the writer has previously stated, there appears to be little if any mortality, operative incidents scarcely mentioned, and the patients inferentially living happily ever after. To make the story complete, this idyllic picture should be embellished with photographs of crutches discarded by these hitherto decrepit, but now obviously rejuvenated individuals.

With some notable exceptions, we seem, as previously stated, to have passed through the era of dogmatic assertion, contentious debate, inane sophistry and muddled conclusion. It must now be obvious that these revolutionary instrumental methods of correction of accomplished prostatic obstruction play a large and ever growing rôle. It has been the occasion of renewed research in open surgery of this gland, with resultant technical improvements, which prior to its advent had been somewhat static. Through its agency many individuals, who will not entertain the thought of open surgery, seem quite willing to submit to instrumental measures, thereby obviating the late sequelae.

It is an incontrovertible fact that after experiencing over a sufficient number of years a blazing cross fire of criticism (a wholesome thing), the enthusiasts, many of whom are in the front rank of urology, are more enthusiastic than ever, the middle-of-the-road group constantly growing in numbers, and the nihilists diminishing. Dr. Omar Elder, one of our beloved colleagues of the South, at a meeting of urologists held some years ago, in his fatherly way said, "Boys, you'd better get aboard this train, because if you don't, it's going to run right over you." To continue the aphorism, it would appear that too many of the boys are riding the cow-catcher. I elect the middle of the train and what seems to me, the right track.

With an enlightened public and an alert profession, the next generation of elderly men should escape the disabilities incidental to prostatic obstruction, as the prevention of this condition by these or similar methods, is altogether feasible.

#### SUMMARY

An effort has been made here to set forth the vicissitudes encountered during the past years, with methods of avoidance, to the end that the profession at large may realize that the prostatic problem, despite the very real progress recently made, is still in a state of flux. This statement is applicable to open surgery as it is to endoscopic methods.

## THE SPECIFIC PREVENTION OF DIPHTHERIA

*Further Observations and Inquiries*

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## THE PROBLEM IN CANADA

PRIOR to the introduction of agents for active immunization against diphtheria, no substantial reduction in the occurrence of that disease was evident in the Dominion of Canada.<sup>1</sup> Despite the fact that diphtheria antitoxin was made freely available to physicians by the public health authorities in almost all parts of the country, for prevention as well as treatment of diphtheria, the recorded morbidity rates maintained their previous high levels. That is not to say, however, that all efforts at control— isolation of cases and quarantine of contacts, separation of other members of the family, and prophylactic antitoxin—were entirely barren of results. The recorded morbidity rates of diphtheria are the resultants of different influences in different periods. For example, environmental changes, such as urbanization of the population, with greater opportunities for human contact, might well have given a real increase in cases in later years in the absence of any control measures, the wider use of laboratory services may have revealed cases otherwise undiagnosed, the use of public health nurses and school nurses may have resulted in more complete notification, and the changing clinical conception of the disease may have included as cases, types which would not have been included in earlier years. While correction cannot be made accurately for such factors, their possible influence on recorded rates cannot be neglected in making comparisons. Be that as it may, the case fatality rates and the specific mortality rates had been falling for over fifty years. But they were still high. From 1920 to 1924 the mortality ranged from 23.2 to 12.8 per 100,000 with 1200 to 2000 deaths or an average of 1600 as the annual toll. Over 40 per cent of that mortality was supplied by the 0-4 age group as shown in Table I. In that period, throughout Canada, diphtheria ranked as the chief cause of death in the

TABLE I  
*Diphtheria deaths Canada registration area\**  
 1921-25

<i>Age</i>	<i>Number</i>	<i>Per cent</i>
Under 1	271	5.8
1	306	6.6
2	397	8.6
3	486	10.5
4	472	10.2
0-4	1932	41.7
5-9	1723	37.2
10-14	611	13.1
15	369	8.0
Total	4635	100.0

\* As Quebec Province did not join the Registration Area until 1926, this table does not include the data for that province

age group 2-14, accounting for over 15 per cent or one in seven of all deaths in that age group <sup>2</sup>

### THE INTRODUCTION OF TOXOID

Not until 1925 was there general agreement among public health workers in Canada in respect of a suitable agent for immunization. In that year, as a result of the work of Ramon, diphtheria "anatoxine" or formol toxoid, prepared in the Connaught Laboratories, University of Toronto, was distributed to the provincial and local departments of health throughout Canada. This was done after careful laboratory and clinical studies had demonstrated its merit on the basis of innocuity and immunizing properties as a specific preventive against diphtheria.

#### *The Reaction Test*

Early experience showed that toxoid causes unfavorable reactions when given to certain individuals. The Reaction test, however, devised by our colleague, Dr P. J. Moloney<sup>3,4,5</sup> made possible the detection of persons who might show untoward reaction if given toxoid. This has eliminated the fear of reactions and thus has greatly facilitated the wide use of toxoid. The Reaction test consists of the intradermal injection of 0.1 cc. of suitably diluted toxoid. A positive reaction, redness, indicates specific sensitivity induced by previous association with the diphtheria bacillus or by artificial immunization. A larger area of redness or, more particularly, of induration at the site is an indication of the likelihood of

that individual showing an untoward sensitivity reaction if given toxoid.<sup>6</sup> Such "reactors" are found mainly among older children and adults. The majority of reactors possess a high degree of antitoxic immunity and the incidence of diphtheria in them is much less than in their unselected controls.<sup>7</sup> It must be emphasized, however, that a positive reaction test in any individual is not proof of immunity. Antitoxin titrations reveal that some reactors have no detectable antitoxin ( $< 1/500$  unit per cc serum). Reactors may be readily immunized with diluted toxoid. In some instances the antigen in the test itself may be sufficient to complete the immunization. The number of positive reactions which may be found depends on several factors—age, diphtheria history and environment, and probably too on the material used. Wide variations in observations made in different places are therefore to be expected.

In Canada diluted toxoid has been used for the past twelve years, with advantage, as a control in the Schick test.<sup>5</sup>

### *The Limitations of the Schick Test*

As the Schick test is used to a great extent in studies in diphtheria, especially in estimating the efficiency of various prophylactics, reference may be profitably made to certain of its limitations. The standards in various countries are not identical. For example, the International Standard and the standards laid down by regulation under the Therapeutic Substances Act of Great Britain and by regulation under the Food and Drugs Act of the Dominion of Canada differ from those prescribed by regulations of the Treasury Department of the United States of America (administered by the United States Public Health Service through the National Institute of Health).

In Table II is shown the disagreement found by using six different Schick tests in eighty-seven individuals.<sup>8</sup> It is evident that among both

TABLE II  
*Antitoxin titres correlated with the interpretation of Schick tests*

<i>Agreement of the 6 Schick readings</i>	<i>Number</i>	<i>Antitoxin Titre</i>					
		$<1/500$	$>1/250$ $<1/100$	$>1/100$ $<1/50$	$1/100$	$>1/50$ $<1/30$	$1/30$ $>1/20$
All positive	33	33					
All negative	24		2	1	1	2	18
Non-interpretable	7	3					3
Frank disagreement	23	6			1	2	14
Total	87	42	2	1	2	4	35

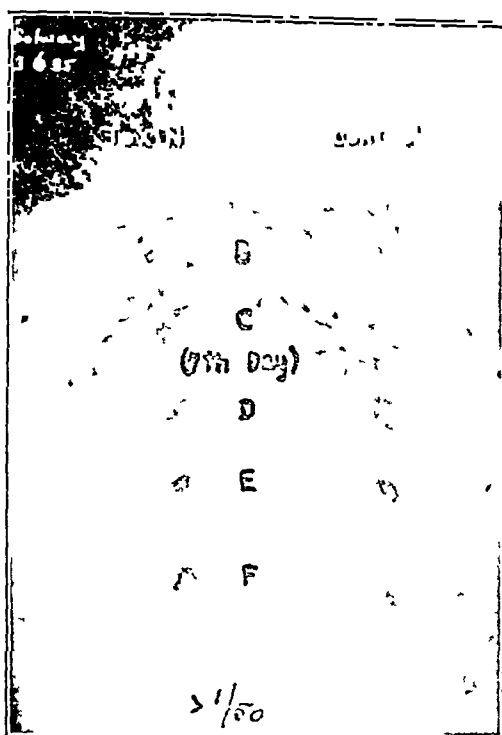


DIAGRAM I

those with high antitoxin content and those with no antitoxin ( $< 1/500$ ) there was frank disagreement in the results. The table also shows that the lowest level of antitoxin associated with a Schick-negative state is about  $1/250$  unit. This is in agreement with the work of others.

In the accompanying illustration, Diagram I, are shown the results of six Schick tests done with six different products simultaneously in one individual who possessed more than  $1/50$  unit of diphtheria antitoxin per cc. of blood serum.<sup>8</sup> The lack of uniformity and the possibility of wrong interpretation need no further comment. Taylor and Moloney<sup>9</sup> have recently analysed fifteen Schick test preparations in regard to toxicity and combining power and correlated the results with the reactions obtained in individuals whose blood serum antitoxin was titrated. Their observations indicate clearly the desirability of revising Schick test requirements.

This must not be construed as undue criticism of the Schick test. It is an instrument which has yielded invaluable information in the epidemiology of diphtheria. Its inherent limitations including its fallacies

TABLE III

*Diphtheria antitoxin response to antigens in children**Per cent distribution by antitoxin levels (units)  
3 months after toxoid*

Group	Antigen	Number Tested	1/500 and >	1/250 and >	1/100 and >	1/50 and >	1/20 and >	1/10 and >	1/5 and >	1/2 and >
1	3 doses, 15-20 Lf (2 cc)	108	99	99	96	94	89	76	52	21
2	2 doses, 50 Lf (2 cc)	105	80	70	60	45	35	*	15	5
3	2 doses, 20 Lf (2 cc)	48	75	60	40	27	8	*	2	0
4	2 doses, 20 Lf (1.5 cc)	48	60	50	29	17	15	*	15	4
5	1 dose alum ppt (1 cc)	40	97	*	67	40	*	15	*	12
6	2 doses alum ppt (1 cc)	36	97	97	97	86	86	39	25	*

\* Not tested at this level

must be understood, however, so that unwarranted conclusions be not drawn from the results obtained

### *Comparison of Antitoxin Response to Various Antigens*

In determining the antigenicity of various prophylactic preparations and in differentiating between them, the Schick test may be of little value.<sup>10</sup> While it will show a difference between a very poor prophylactic and a good one, it will not differentiate between two of a higher order of efficiency. For such differentiation, titrations of the blood antitoxin, as recommended by Fraser,<sup>11, 12</sup> give much more reliable and complete information.

For full details in this connection reference should be made to the original publications. In Table III are shown the antitoxin responses induced by various prophylactic procedures.

It must be emphasized that these comparisons were made in children whose complete susceptibility was established prior to being given the prophylactic. In Group one the Schick test and Reaction test were used to select the children and all were frankly Schick-positive and Reaction test negative. In the other groups, antitoxin titrations of blood serum showed that all had initially less than 1/500 unit. This is, we think, most significant, as it is essentially for such individuals that prophylaxis is necessary. The suggestion that one or two doses of alum precipitated toxoid will give as satisfactory antitoxin response as that induced by three doses of unmodified toxoid is not borne out by these results.

Even more striking is the difference found in the duration of high antitoxin content, as shown in Table IV.

It is evident that at approximately one year after being given three

TABLE IV

Comparison of antitoxin titre after

A—1 dose alum precipitated toxoid B—3 doses unmodified toxoid  
Original titre  $<1/500$

Per cent with	After					
	10 weeks		10-14 months		22-25 months	
	A	B	A	B	A	B
01 or $>$ units	68	91	22	97	15	86
02 or $>$ units	40	91	14	75	15	76
Number of children	40	35	36	32	26	21

doses of toxoid, over 90 per cent of thirty-two children still had  $1/100$  unit or more per cc of blood serum in contrast to but 22 per cent retaining this level in a group of thirty-six children who had been given one dose of alum precipitated toxoid. At a two-year period the percentages showing  $1/100$  unit or more of antitoxin are eighty-six and fifteen for those given three doses of unmodified toxoid and one dose of alum precipitated toxoid respectively. The numbers of children in this comparison are not great, but the difference is far beyond chance variation.

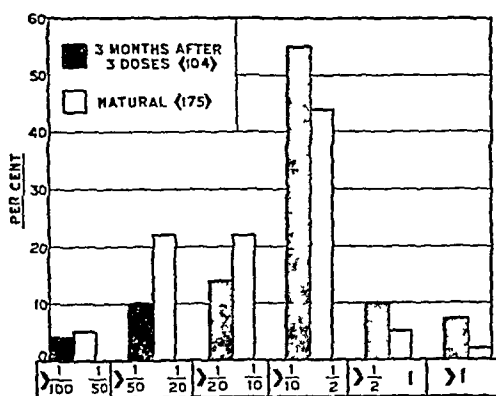


DIAGRAM II

Distribution by antitoxin levels of naturally and artificially immune persons

### Gradual Decline in Antitoxin Content after Vaccination

It is gratifying to learn from Diagram II that the antitoxin content induced by three doses of toxoid is fully comparable and indeed slightly above that found in a sample of naturally immune persons. But it is as important, though less pleasant, to realize that as time passes after immunization, the level of antitoxin tends to fall. Fraser and Halpern have

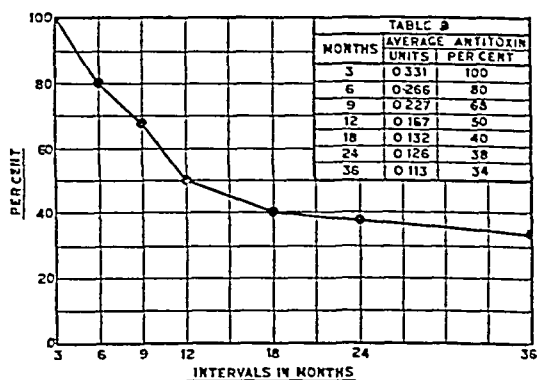


TABLE V

Per cent antitoxin at intervals compared with the initial amount three months after three doses of toxoid

made antitoxin titrations in groups of children at various time intervals after three doses of toxoid. In this way one is able to obtain data not only on the levels of antitoxin of the individual but also on the average unitage of the group at specified intervals of time.

Table V shows the average (unitage) of each group at the intervals indicated and the percentage compared with the amount at the three-month period. These percentages are shown in the graph. At the one-year interval the average antitoxin content of the group as a whole is 50 per cent of the former level. It is of interest to note that the rate of loss is progressively less after twelve months. It will be realized that marked variations in the rate of loss of antitoxin will be found among individuals and that the rate may be changed significantly by the amount of diphtheria in the environment. In certain instances, if such chance contact with diphtheria bacilli be sufficient, the antitoxin may be increased, as shown by Fraser and Halpern. It must be pointed out that the results shown in Table V were obtained from the titrations of blood sera of children living in an environment practically free from diphtheria. Only in five instances was there evidence of increase in antitoxin content during the time of observation.

In a word, from the data quoted, it can be said that three doses of toxoid yield a higher level of antitoxin response and thus more durable antitoxic immunity than any other procedure compared to date, that the level induced by three doses of antitoxin is fully comparable with that found in natural immunes, but that this level tends to fall as the years pass following immunization.

TABLE VI

*Reduction in Diphtheria in school children subsequent to toxoid,  
Toronto public schools, 1926-1930*

<i>Doses of Toxoid</i>	<i>Cases</i>		<i>Percentage Reduction</i>	<i>Deaths</i>
	<i>Estimated*</i>	<i>Actual</i>		
One dose	34	24	29	3
Two doses	200	52	74	2
Three doses	222	23	90	0

\* At rate in controls (schoolmates) under same exposure, corrected for age, etc

### *The Protection against Diphtheria afforded by Toxoid*

It is pertinent now to inquire into the actual value of toxoid in protecting children against diphtheria. For this purpose we have the amount of the diphtheria that occurred in children given one, two and three doses of toxoid, in comparison with the diphtheria in their school mates in Toronto public schools under the same exposure, as shown in table VI.<sup>7</sup>

These observations were made when diphtheria was still very prevalent and represent therefore the results under conditions of high exposure. The group numbered over 27,000 children, while the controls were the balance of the school population, approximately 90,000. The adequacy of one dose is at once apparent. The advantage of a second dose in immunization is evident in the greater reduction (74 per cent) of diphtheria in those given two doses of toxoid. The superiority of three doses is evident in the 90 per cent reduction of cases in the 16,829 children given three doses of toxoid in the 1927-1930 period. The difference in the results of two doses and three doses is beyond chance variation and statistically significant. Further, and of importance, this difference is in general agreement with the difference in antitoxin responses induced by two or three doses of toxoid.

These observations were extended to include other school children given three doses of toxoid subsequent to 1930, making a total of 46,000, with the results shown in Table VII.<sup>13</sup> In each year the reduction in diphtheria in the group given three doses of toxoid approximated 90 per cent. In other words, this group suffered but 10 per cent of the rate of diphtheria suffered by their seat-mate controls. The study suggested, however, that as time passed after vaccination there was some falling off

TABLE VII

*Reduction in diphtheria in children given three doses of toxoid  
Toronto public school, 1927-1932*

Year	Cases		Percentage Reduction	Deaths
	Estimated*	Actual		
1927-1928	25	1	96	0
1928-1929	81	7	92	0
1929-1930	113	15	87	0
1930-1931	133	14	89	0
1931-1932	105	3	97	0
1927-1932	460	40	91	0†

\* At rates in controls under the same exposure, corrected for age, etc

† To the end of December 1937 there has been but one death from diphtheria in any child given three doses of toxoid in Toronto. This occurred in September 1935 in a child six and one-half years old who had been given three doses of toxoid five years previously.

in the degree of protection. This is entirely in keeping with the falling off in antitoxin content as shown by Fraser and Halpern and is additional evidence that immunity to diphtheria is a function of antitoxin. As is shown in Diagrams IV and V, subsequent to 1932 the paucity of diphtheria in Toronto yielded figures so small that deductions from them in regard to protection afforded by toxoid to vaccinated individuals were impractical.

### *The Control of Diphtheria Morbidity and Mortality*

Gratifying as is the 90 per cent reduction in diphtheria in those given three doses of toxoid, as compared with their unvaccinated schoolmates, the actual benefit is not confined to those vaccinated, but is reflected in a reduction in diphtheria among their associates.

From 1925 to 1936 inclusive, sufficient toxoid has been distributed from the Connaught Laboratories for the immunization of over three million persons in Canada. It is not known precisely how much has been used, but the effect is evident in the strikingly lower rates of diphtheria morbidity and mortality in various cities and provinces in Canada. Diagrams III to VI are illustrative.

In Table VIII and Diagram III the history of diphtheria in the province of Ontario is briefly recorded. The population has increased from under two million in 1880 to over three and one-half million in 1936. In 1916 the Provincial Board of Health of Ontario provided for completely free distribution of diphtheria antitoxin. There were avail-

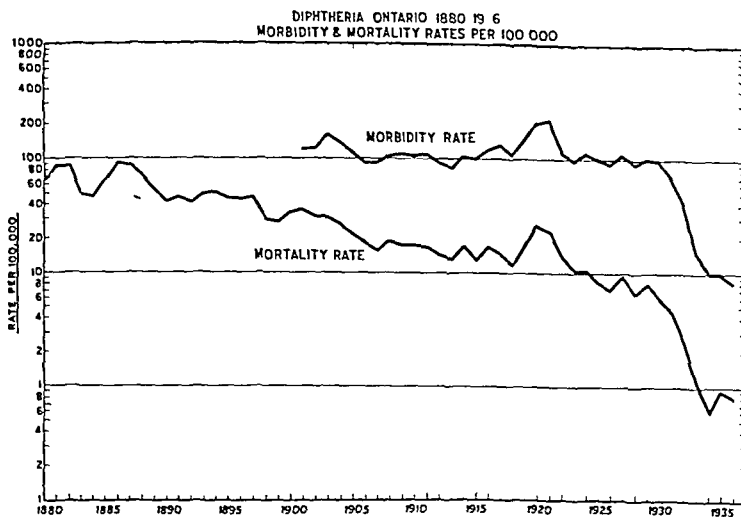


DIAGRAM III

ble at the time, for physicians in Ontario, very satisfactory public health diagnostic laboratory facilities to aid in the diagnosis of diphtheria. Thus for more than three millions of persons the scientific weapons available twenty years ago, for the prevention and treatment of diphtheria, were readily accessible. Furthermore, physicians and the general public were repeatedly urged to take advantage of these facilities. In spite of that fact, as has already been indicated, the free use of diphtheria antitoxin, while it may have influenced diphtheria mortality and case-fatality rates, showed little or no effect on the absolute volume of recorded diphtheria morbidity, and the essential lack of control of the disease is seen in the return to the high mortality rate of over 25 per 100,000 in 1920 and in the sustained high level of recorded morbidity, even after allowing for changing influences, for nearly thirty years when there is a precipitous decline such as had not occurred in the previous thirty years for which morbidity records are available, or in the previous fifty years for which mortality records are shown. From a rate of 97 in 1930, morbidity fell to 10 per 100,000 in 1934, and from a rate of 6 per 100,000 in 1930—the lowest on record till that date—mortality fell to 0.6 per 100,000 in 1934. This change has followed the extensive use of toxoid. The abruptness of the change in the picture coupled with the established efficiency of toxoid leaves no room for doubt that the change is due to active immunization. Any other hypo-

## TABLE VIII

*Diphtheria Ontario 1880-1936*

Year	Deaths	Mortality Rate per 100,000	Year	Cases	Deaths	Mortality Rate per 100,000	Morbidity Rate per 100,000	Cases Fatalities Rate per 100 Cases
1880	1251	66.0	1901	2,627	772	35.4	120	29.4
1881	1704	88.4	1902	2,696	676	30.5	122	25.1
1882	1708	87.8	1903	3,599	687	30.5	160	19.1
1883	976	19.7	1904	3,015	608	26.6	133	20.0
1884	929	16.8	1905	2,611	503	21.7	114	19.1
1885	1282	64.0	1906	2,116	423	18.0	90	20.0
1886	1833	90.7	1907	2,172	380	15.9	91	17.5
1887	1786	87.6	1908	2,477	450	18.6	102	18.2
1888	1459	70.9	1909	2,635	430	17.5	107	16.3
1889	1101	53.0	1910	2,559	435	17.5	103	17.0
1890	893	42.6	1911	2,631	423	16.7	104	16.1
1891	952	45.0	1912	2,310	371	14.4	91	15.8
1892	890	41.9	1913	2,194	339	13.0	84	15.4
1893	1044	49.1	1914	2,772	443	16.7	105	16.0
1894	1075	50.3	1915	2,719	341	12.7	101	12.5
1895	912	44.0	1916	3,212	461	16.9	118	14.3
1896	925	43.1	1917	3,590	396	14.3	129	11.0
1897	976	45.3	1918	3,093	335	11.9	110	10.8
1898	634	29.3	1919	4,261	475	16.7	149	11.1
1899	599	27.6	1920	5,940	745	25.7	205	12.5
1900	738	33.9	1921	6,313	653	22.3	215	10.3
			1922	3,529	411	13.8	118	11.6
			1923	2,935	316	10.4	97	10.8
			1924	3,473	322	10.5	113	9.3
			1925	3,031	251	8.1	98	8.3
			1926	2,818	227	7.2	90	8.1
			1927	3,346	297	9.3	105	8.9
			1928	3,918	213	6.6	90	7.3
			1929	3,261	262	8.0	100	8.0
			1930	3,198	202	6.1	97	6.3
			1931	2,368	157	4.6	69	6.6
			1932	1,496	89	2.6	43	5.9
			1933	529	40	1.1	15	7.6
			1934	371	23	0.6	10	6.2
			1935	361	33	0.9	10	9.1
			1936	290	31	0.8	8	10.7

thesis to explain the change is superfluous. The fact that diphtheria has declined proportionately more than might have been anticipated from the number given to void is not difficult of explanation. Reducing cases in the immunized reduces foci of infection, spreaders of disease, in the group as a whole, so that the non-immunized benefit indirectly, this makes the control of diphtheria eminently practical. Further evidence of this is presented on page 578.

Hamilton, Ontario, a city of 150,000 population, was the first city of that size in Canada to control diphtheria effectively.<sup>14</sup> The achievement of Dr. James Roberts, Medical Officer of Health of Hamilton has been a fine incentive to others. The record of this control is shown

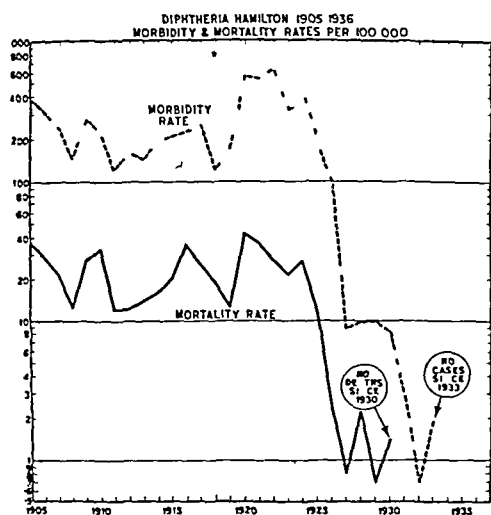


DIAGRAM IV

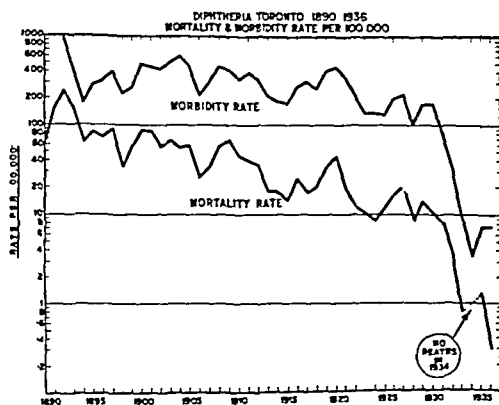


DIAGRAM V

in the above diagram (IV) There have been no deaths since 1930 and no cases since 1933 This record speaks for itself

Diagram V shows the history of diphtheria in Toronto, Canada, a city of approximately 650,000 population Since 1926, 104,000 children have been given three doses of toxoid by physicians of the Department of Public Health It is estimated that 13,000 children have been given toxoid by their own physicians The effect of this continued immunization is shown in the abrupt change in diphtheria, the morbidity rate falling from 164 per 100,000 in 1930 to 3.5 in 1934 In pre-toxoid years the annual toll was forty-five to ninety-eight deaths, an average of sixty-five from 1921 to 1925 For a period of fifteen months, from January 1934 to March 1935, not one death from diphtheria occurred in the city \*

The records of other smaller cities in Ontario, for example, Brantford, population (1936)—31,382, show even more satisfactory control of the disease

Since 1922 free diphtheria immunization has been provided No case of the disease has been reported since November 18th, 1930 Of the children born in 1937, 91 per cent have already received diphtheria toxoid

Montreal, Quebec, a city of nearly 1,000,000 population, has experi-

\* In the calendar year 1937, for the second time, no diphtheria death was reported in Toronto

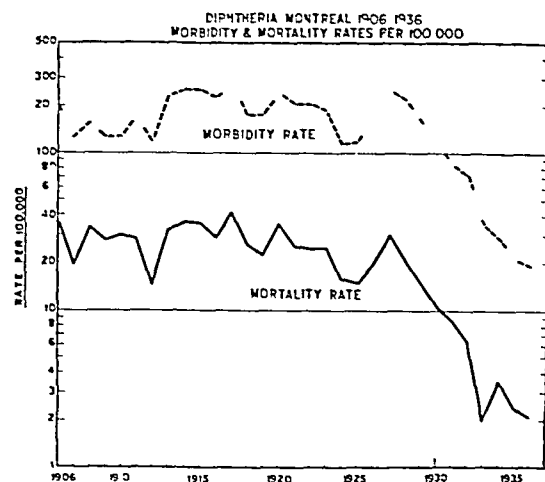


DIAGRAM VI

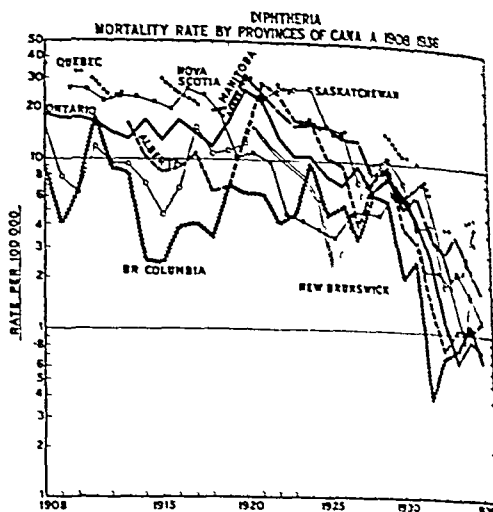


DIAGRAM VII

enced a similar decline in diphtheria following the extensive use of toxoid, as shown in Diagram VI\*

Diagram VII is given to show that every province of Canada has shared, though not equally, in the decline in diphtheria following the use of toxoid

### *Reduction in the Incidence of Carriers*

It has been suggested that specific immunization against diphtheria may occasion an increase in the carrier rate of virulent diphtheria bacilli in any community. Deadman<sup>15</sup> showed in 1932 that the experience in Hamilton, Ontario, was not at all in conformity with this suggestion. In 1920, 8261 cultures were examined for the diphtheria bacillus in his laboratory, 1040 were positive. In 1921, 9645 were examined and 1234 were positive. These data were typical of that time. In 1932, 3929 were examined and eighty-five (from twelve individuals) were positive. In 1934, out of 3817 examined, none were positive. Again in 1936, out of 3949 examined, none were positive.

From May 1934 to June 1936 surveys were made in Toronto in which approximately 7800 nose and throat cultures from the school children were examined.<sup>12</sup> Only four were found to contain virulent diphtheria bacilli. In another group of 999 children in an adjacent municipality, partly urban and partly rural, only two diphtheria carriers were

TABLE IX  
*Diphtheria, Toronto*

<i>Year</i>	<i>Cases</i>	<i>Deaths</i>	<i>Number Examined</i>	<i>Positive Swabs</i>	<i>Summation of Persons Immunized*</i>
1926	1098	90	13,231	2564	
1927	1223	111	12,286	1661	80
1928	593	50	9,354	827	12,492
1929	1030	82	16,542	2754	17,564
1930	1085	66	13,501	2109	18,954
1931	564	49	9,728	1086	35,280
1932	180	22	6,760	258	57,890
1933	58	5	5,077	86	72,367
1934	22	0	4,516	28	85,870
1935	46	8	4,322	56	92,918
1936	48	2	4,307	80	104,449

\* Population 1926—556,691

1936—645,462

Immunized—given three doses of toxoid

discovered. In surveys of 1774 school children in Montreal in 1935-37, only two carriers were detected. Table IX shows the numbers of positive cultures found in routine work in the laboratories of the Department of Public Health in Toronto.

It is evident that in spite of a much greater number of cultures examined in relationship to the number of cases and a much more diligent search of the population, the number of carriers found showed very striking reductions. There is thus no evidence in these data in support of the suggestion that immunization of part of a community increases the hazard of diphtheria.

A comparison of the incidence of diphtheria in Canada, where vaccination against the disease has been widespread, with England and Wales, where a very limited amount of specific prophylaxis has been applied, is illustrated in Table X. It will be observed that for the weeks in 1937 and 1938 which are compared, the notified incidence of the disease in England and Wales is four to five times greater than has been recorded in the Dominion of Canada.

#### SUMMARY AND CONCLUSIONS

Prior to the use of toxoid there was no effectual control of diphtheria in Canada. In spite of the free distribution of antitoxin for prevention as well as treatment, recorded diphtheria morbidity persisted at its previous high levels, and mortality, though falling, still presented one of the most important public health problems.

TABLE X

*Diphtheria cases reported Aug 21, 1937 to Jan 29, 1938*

These rates are based on the estimated populations for 1936

England and Wales—10,839,000

Canada —11,014,000

Week ending	England & Wales		Canada	
	Cases	Rate per 100,000	Cases	Rate per 100,000
Aug 28	910	2.2	30	0.3
Sept 4	1084	2.7	58	0.5
Sept 11	1241	3.0	43	0.4
Sept 18	1308	3.2	81	0.7
Sept 25	1320	3.2	71	0.6
Oct 2	1318	3.3	67	0.6
Oct 9	1451	3.5	80	0.7
Oct 16	1566	3.8	82	0.7
Oct 23	1706	4.2	104	0.9
Oct 30	1694	4.1	106	0.9
Nov 6	1698	4.1	99	0.9
Nov 13	1750	4.3	117	1.1
Nov 20	1634	4.0	92	0.8
Nov 27	1830	4.5	120	1.1
Dec 4	1765	4.3	119	1.1
Dec 11	1683	4.1	92	0.8
Dec 18	1568	3.8	76	0.7
Dec 25	1291	3.2	73	0.7
Jan 1	1417	3.5	77	0.7
Jan 8	1584	3.9	57	0.5
Jan 15	1659	4.1	78	0.7
Jan 22	1737	4.3	74	0.7
Jan 29	1892	4.6	107	1.0

The Reaction test, as devised by Moloney, practically obviated the hazard of reactions and thus facilitated the wide use of toxoid.

Requirements for the Schick test are in need of revision and standardization. It is not infallible and its limitations should be recognized.

For determining the antigenicity of and differentiating between prophylactics the Schick test may be of little value. Antitoxin titrations give more complete and reliable information.

Titration of the blood serum of children who initially had no antitoxin and were then submitted to various immunization procedures show that three doses of unmodified diphtheria toxoid induced a higher antitoxin response than any of the other procedures compared, namely, two doses of unmodified diphtheria toxoid, one dose of alum precipitated toxoid and two doses of alum precipitated toxoid. Titrations of blood serum of vaccinated children indicate a loss in antitoxin as time passes.

Field studies show that the reduction in diphtheria, in those vaccinated with two doses of toxoid, is, like the antitoxin response, less than the reduction in those vaccinated with three doses and that the diphtheria

occurring in the latter group is reduced by approximately 90 per cent as compared with that found in schoolmates under the same exposure

Records show striking declines in diphtheria morbidity and mortality and in the incidence of carriers in various cities and provinces in Canada following the wide use of toxoid

The abruptness of this decline in diphtheria morbidity and mortality and in the instance of diphtheria carriers in Canada following the extensive use of toxoid, the absence of any comparable diminution in the number of cases or of deaths from diphtheria prior to the use of toxoid, and the demonstrated efficiency of toxoid in preventing diphtheria in those vaccinated, leave no doubt that the decline is due to immunization

The extent of the decline in several of the large cities and in certain of the provinces of Canada shows indubitably that diphtheria is a preventable disease

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BULLETIN OF  
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OCTOBER 1938

STUDIES ON THE CORTICAL  
REPRESENTATION OF SOMATIC SENSIBILITY

*Harvey Lecture, February 17, 1938*

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THE information at present available concerning the representation of somatic sensibility in the cerebral cortex is admittedly fragmentary. This state of affairs is doubtless due to the peculiar difficulties which attend all investigations of sensory functions. Extensive experiments can be carried out with proper control procedures in animals, but here the interpretation of results is often made difficult by the fact that it is not always easy, in the absence of a verbal report, to distinguish between a motor and a sensory deficit, and to consider sensation in an animal is to draw an inference which, however plausible, has no place in objective physiological work. While clinical studies in this field possess the great advantage that they permit an examination of sensory experience, they suffer from the fact that the nature of the material greatly limits the range of experimentation.

In the exploration of the somatic sensory functions of the cortex a number of methods have been used. Some idea of the areas concerned has been gained by inference from the distribution of thalamocortical

fibers mediating deep and cutaneous sensibility After interruption of these at or near the thalamus, Poliak<sup>1</sup> traced their degeneration into the cortex His results in the monkey indicate that the somesthetic projection area is a large one extending "about equally, orally and caudally, from the sulcus centralis as well as over the internal face of the hemisphere where it reaches the sulcus cinguli" By studying the retrograde degeneration in the thalamus following removal of one or another part of this area Clark and Boggon,<sup>2</sup> Walker<sup>3</sup> and others have added important details to our anatomical knowledge of this representation The interpretation of these findings in terms of function is one of the pressing problems confronting neurophysiologists

In the clinical studies of this subject the most definite results have been obtained by stimulating the exposed cortex of the human subject in the course of operative procedures not involving a general anesthetic This method was early used by Cushing<sup>4</sup> to study sensation, and more recently others, notably Foerster<sup>5</sup> and Penfield,<sup>6</sup> have published detailed maps of the somesthetic representation indicated by it The results obtained by different neurosurgeons have on the whole been in fair accord as regards the sequence of the representation of the parts of the body, but there is some disagreement about the question of bilateral representation and the matter of overlap of sensory and motor areas<sup>6</sup> A valid criticism of this method is that application of a stimulating current to tissue of such histological complexity cannot be expected to give the same result as the arrival of definitely grouped corticopetal nerve impulses This is doubtless reflected in the nature of the sensations experienced by the subjects Most frequently numbness and tingling, only rarely definite sensations comparable to those experienced in normal life, are reported In brief, the cortical stimulation experiments have yielded much important information regarding the locus of representation, but have told us little about the sensory modalities represented

Many studies of the effects of cortical ablations and lesions upon sensory functions have been made Much of the clinical work has suffered seriously from inability to determine the exact extent of the lesion In the experiments on animals difficulties have arisen from the fact that usually the only available criterion of a sensory disturbance following an ablation is a failure of or a deficiency in some motor performance Therefore, if the sensory modality under investigation is one which is represented in the cortical area governing the motor act, the ablation

method is useless. This point is emphasized in view of the evidence indicating that the region of the motor cortex subserves certain sensory functions.<sup>6,7,8</sup> When, however, it can be shown that the cortical sensory and motor mechanisms subserving an act are spatially separate the method may yield illuminating results.

Significant results bearing on the problem of the somatic sensory functions of the cortex have been obtained in animal experiments by the method of local strychninization. Dusser de Barenne<sup>7</sup> has shown that the local application of strychnine to certain parts of the cortex of cats and monkeys produces signs of marked hyperexcitability of the skin to tactile, thermal and nociceptive stimuli and of the deeper structures to pressure. In the monkey the cortical area in which the local application of the drug produces symptoms of hyperesthesia covers not only the entire parietal lobe, but also the precentral regions as far forward as the arcuate sulcus. It includes areas 4 and 6, which are important motor projection areas, as well as areas 3, 1, 2, 5 and 7. The symptoms of sensory excitation indicate that the cutaneous sensibility of both sides of the body is represented in each cortex, while deep sensibility is chiefly represented in the contralateral cortex. The action of strychnine fails to bring out the detailed localization which other methods have revealed, the cortical zone is divisible only into leg, arm and face areas. The application of strychnine to a few square millimeters within any one of these three gives rise to the same hypersensibility as strychninization of any other similar fraction of that area. Dusser de Barenne has always explained this on the basis of the assumption that strychnine causes a spread of excitation through the whole of the area, and recently in work with McCulloch<sup>9</sup> he has secured direct evidence of the correctness of his explanation. As Dusser de Barenne has pointed out, strychnine in bringing out the maximum of sensory function obscures the finer functional differentiations. This is the chief limitation of the method. It has, however, delimited a large area into which, it is reasonable to suggest, future work will have to fit the details, functional and anatomical, of the total cortical representation of each modality of somatic sensibility.

The problem of the representation of somatic sensibility in the cerebral cortex is one which, in spite of more than sixty years of experimental attacks upon it, still demands that attention be given the matter of locus. Until this aspect of the problem has been further elucidated it is likely that considerations of the intimate nature of the cortical

mechanisms involved will prove delusive. It was with this point in mind that the experimental work which forms the basis of this lecture was undertaken. Two methods have been employed, one of them old, the other quite new. It was hoped that each might give information bearing on the important question whether the different modalities of cutaneous and deep sensibility have cortical representations which are spatially separate, but in this respect our work to date has been disappointing. I am able, however, to report results which appear to give precise information concerning the locus of cortical mechanisms subserving tactile sensibility.

## I. SENSORY COMPONENTS IN THE CORTICAL MANAGEMENT OF THE PLACING AND HOPPING REACTIONS

The fact that in the monkey certain postural reactions are dependent on the cerebral cortex has permitted the analysis which forms the first part of this lecture. The simplicity of these motor acts, their uniform presence in normal animals and their easy elicitation by specific stimuli make them singularly favorable instruments for the study and delimitation of the cortical control. In the course of a series of experiments designed to delimit the central management of these reactions Woolsey and I<sup>10</sup> have been able to secure certain information concerning the cortical representation of the sensory modalities involved in their elicitation. The responses are the placing and hopping reactions which were first described by Rademaker<sup>11</sup> and which have been further studied in several groups of animals by the lecturer and his collaborators. Of special significance in the present discussion are those placing reactions which are evoked by tactile stimulation and the hopping reactions. The latter are proprioceptive in origin.

*The Placing Reactions*—A primary requirement for normal standing is that the feet should be placed in the proper position. To a considerable extent the normal monkey accomplishes this through the agency of the following reactions:

1. When the animal is moved toward a supporting surface visual stimuli cause the feet to be put down in such a way that without further adjustment they can support the body in standing. If the movement of the body is downward and sufficiently rapid vestibular stimuli will bring about a similar response. Although we have made a study of the central control of these visual and vestibular placing reactions, our results are irrelevant for the purposes of the present discussion and will not be given.

The remaining placing reactions can be elicited in pure form only when visual placement is excluded by blindfolding or by removal of the occipital lobes.

2. If the animal is held in the air with legs free and dependent, the slightest contact of any portion of the hand or foot with the edge of a table results in either an immediate

and accurate placing of the palm or sole on the table or a grasping of its edge by fingers or toes. This response is usually followed immediately by placing of the unstimulated opposite hand or foot (cross-placing).

3 If with arms free, the chin, lips, sides of the jaw, or merely the hairs of the face are brought into light contact with some supporting surface both hands are instantly raised and placed on the source of the stimulus. Occasionally the feet are also placed. When the arms are held such stimulation causes the feet to be brought up and placed.

4 When the arms or legs are thrust over the edge of a table on which the animal is standing, lying or sitting they are immediately lifted so that their original position on the table is regained. (Since both tactile and proprioceptive stimuli may enter into the elicitation of this reaction we have not used it in our attempt to solve the problem under consideration.)

5 A proprioceptive placing reaction of the limb may be evoked in animals in which reaction 2 has been differentially abolished by appropriate surgical procedures, e.g., parietal lobectomy. In such preparations contact of the apical portions of the limb with a table edge does not of course evoke placing. When, however, forward displacement of the body has induced a considerable degree of retroflexion at shoulder or hip, the hand or foot is lifted, carried forward and placed far inside the table edge. This is a reaction which Rademaker termed a proprioceptive correcting movement of the limb.

*The Hopping Reactions*—These are specific corrective movements of the limbs which serve to maintain a standing posture under conditions involving displacement of the body in the horizontal plane. They may be demonstrated by holding the animal so that it stands on one arm or one leg. Then on moving the body forward, backward or to either side, the limb hops in the direction of the displacement so that the hand or foot is kept directly under shoulder or hip. When displacement of the body induces in the limb a deviation from the normal median perpendicular position the supporting tone of the muscles around the proximal joints diminishes, the limb is flexed, moved in the direction of the displacement, and the apical portion put down again to give a median support for the body in its new position.<sup>11</sup> Thus the hopping reactions, like the placing reactions, serve to put the feet in the normal position for standing, but they also contribute to the maintenance of equilibrium. The nature of the postural changes which induce these specific responses suggests that they are proprioceptive in origin. According to Rademaker and Hoogerwerf<sup>12</sup> the adequate stimulus is actually a stretching of one or another group of muscles. Whether or not sense organs in joints or tendons are concerned is a question which has not been decided. Our observation that hopping in the leg can be evoked by body displacement after complete denervation of all parts below the knee shows clearly that these responses are not dependent on contact or deep pressure, but are evoked by stimulation of proprioceptors in the proximal portion of the limb. We feel fully justified in using them as criteria of the operation of a central controlling mechanism which is thrown into action by afferent impulses from proprioceptors.

*The Comparative Physiology of the Reactions*—In the reptile (alligator, lizard) placing in response to tactile stimulation does not occur, but proprioceptive placing and hopping reactions are present. These depend upon central mechanisms lying below the telencephalon.<sup>13, 14</sup> In the rat and rabbit reactions similar to those described above occur, but they are less well developed, and on decortication all placing reactions in response to tactile stimulation disappear, but the hopping reactions are only slightly disturbed.<sup>15, 16</sup> In the cat and dog removal of cortex produces a similar but more complete deficit.<sup>17, 18</sup> Thus in the ascending scale of vertebrate quadrupeds the central control of these particular responses becomes more and more "corticalized." In the subprimate mammals it has been found that the cortical management of the reactions of the legs of one side is spatially limited to the sensorimotor area of the opposite hemisphere, a maximal cortical deficit is produced by ablation of this area alone while removal of all cortex except the



Fig 1—Four frames from a motion picture film taken fifteen months after removal of areas 4 and 6 of the left cerebral cortex. A-D show stages of the normal placing reaction of the left arm which occurs when the backs of the fingers are brought into slight contact with the edge of a table. Note that the response fails to occur in the arm contralateral to the cortical ablation (Woolsey and Bard<sup>10</sup>)

sensorimotor zone leaves the responses unimpaired.<sup>15,1</sup> Because of the more highly developed cortex of the monkey it has been possible to extend the study of these reactions beyond the task of delimiting the total area of cortex concerned in their control to an analysis of the respective rôles played by the cortical motor and sensory components.

*Experimental Results*—After hemidecortication in the monkey all these responses except the labyrinthine placing reactions (which become greatly deficient) are totally and permanently abolished in the contralateral limbs, while those of the ipsilateral extremities remain entirely normal. With this as an established fact experiments were carried out to determine just which cortical areas are concerned. It was found that unilateral removals of (a) all cortex rostral to the central fissure, i.e., the frontal lobe, or (b) areas 4 and 6 together, or (c) the cortex corresponding to Brodmann's representation of area 4, cause enduring loss of all contralateral reactions except the visual and labyrinthine which are

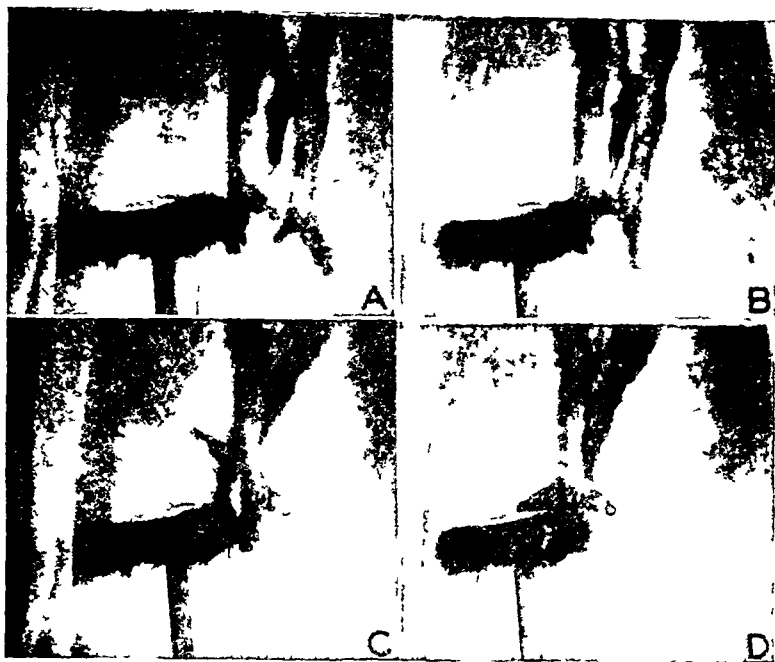


Fig 2—A contact cross-placing reaction in the monkey shown in Fig 1. Because of the absence of area 4 of the left cortex the right foot is not placed when it is touched to the edge of the supporting surface, but this tactile stimulus elicits placing of the left foot, a response which, as explained in the text, depends on the integrity of the left postcentral gyrus (Woolsey and Bard<sup>10</sup>)

retained in modified form. Incomplete extirpations of area 4 (as outlined by Brodmann) or removal of both banks of the central fissure (Polak's focal sensory zone) produce permanent deficiencies but not complete losses.

When a unilateral *precentral* ablation has produced a complete loss of the placing reactions of the opposite limbs it is still possible (in a blind-folded animal) to obtain placing of the sound (the ipsilateral) hand or foot by bringing the deficient (the contralateral) members into slight contact with the edge of a table. We have termed this response a *contact cross-placing reaction* (Fig 2). Its occurrence indicates that a light tactile stimulus is appreciated although the motor responses of the stimulated members are completely deficient. Obviously the disappearance of the contralateral contact placing reactions which follows removal of the entire frontal lobe or of area 4 represents a motor rather than a sensory

loss Since contact cross-placing reactions cannot be obtained after complete hemidecortication it appears that they depend on postcentral cortex In fact they depend on the postcentral gyrus and it may be supposed that the cortex of this region, on receiving afferent impulses originating at the surface of the contralateral half of the body, somehow brings into action the motor cortex of the opposite hemisphere To date we have been unable to secure any evidence that there is an ipsilateral cortical representation of the type of sensibility necessary for the contact cross-placing response

The all-important rôle of the postcentral gyrus in the central mediation of placing reactions evoked by light contact (tactile stimulation) is clearly shown by the results of its removal After such an operation (also of course after unilateral parietal lobectomy or removal of all cortex except the frontal lobe) an appropriate contact stimulus applied to the hand, foot or jaw of the opposite side causes neither placing nor cross-placing This loss is permanent and entirely contralateral, the reactions of the ipsilateral limbs evoked from that side remain normal That the deficiency is not the result of impairment of the cortical motor mechanism is demonstrated by this fact When the side of the face opposite the intact hemisphere is given an appropriate tactile stimulus while the limbs of that side are held, the limbs contralateral to the ablation engage in a perfectly executed cross-placing response This reaction is a phenomenon which has permitted us to demonstrate a spatial separation of the motor and sensory components of the cortical mechanisms essential for the placing reactions evoked by tactile stimulation Cross-placing depends on some functional connection between the postcentral gyrus of one hemisphere and area 4 of the opposite side It is of interest that complete division of the corpus callosum fails to abolish or in any way to modify the cross-placing reactions

Although ablation of the postcentral gyrus completely and permanently abolishes the possibility of inducing placing reactions in response to tactile stimulation of the opposite side, hopping reactions are only temporarily if at all affected After such an ablation and even after removal of all cortex except the frontal lobe they soon return to normal, and then proprioceptive placing can also be elicited Many experiments have afforded evidence that removal of all cortex lying rostral to area 6 does not affect either hopping or placing The conclusion that the entire cortical management of these proprioceptive responses is situated rostral

to the central fissure seems justified in view of two additional facts (a) removal of the second parietal lobe does not affect the reactions and (b) proprioceptive cross-placing cannot be obtained after hemidecortication. If there is a sensory component in the cortical control of the hopping and proprioceptive placing reactions it must be precentral in location and therefore anatomically quite separate from the sensory cortical mechanisms essential for the tactile placing reactions. We have, however, been unable to demonstrate any topographical division of the cortical management of these proprioceptive reactions into sensory and motor parts. The identification of a sensory element here would permit the conclusion that the two types of sensibility (tactile and proprioceptive) involved in these two groups of postural reactions have separate representations in the cortex. Although it seems probable that a sensory element enters into the cortical control of hopping and proprioceptive placing, there remains the possibility that the motor region may act merely by facilitating through tonic efferent discharge a subcortical mechanism and that the withdrawal of this influence on removal of area 4 abolishes these responses by raising the threshold of the subcortical center to proprioceptive impulses.\* It is certainly most unlikely that in the evolutionary process which has resulted in corticalization of the control of these reactions the ancient subcortical mechanism apparent in reptiles and discernible in decorticate rabbits, rats and carnivores has been bodily lifted into the cerebral cortex. Indeed its existence in the monkey can be demonstrated. Here, as already mentioned, removal of area 4 or hemidecortication completely abolishes the hopping reactions of the opposite legs, no return is seen during postoperative periods of from one to three years, and in this sense the functional loss is permanent. Yet if in any of these preparations the intact cerebral hemisphere is subjected to an ablation which includes area 4, poor but definite hopping reactions can be elicited at once in the legs contralateral to the original lesion and later in the ipsilateral limbs. Woolsey has observed this phenomenon in a completely decorticate monkey which to date has survived removal of the second cortex for more than four months.

In an earlier communication<sup>17</sup> it has been urged that a true measure of the degree of cortical localization of any function can be obtained only by determining how much cortex may be removed without disturbing the function in question. In attempting to apply this principle to the present

\* This possible explanation of the role of the motor cortex in the central control of the hopping reactions was first suggested to the writer by Dr. Warren S. McCulloch of Yale University.

problem we found that ablation of all cortex of the frontal lobe lying rostral to area 4 or extirpation of occipital and temporal lobes together has no permanent effects on the hopping reactions and the non-visual placing reactions. When both removals were carried out in the same hemisphere the remnant, consisting of areas 4, 3, 1, 2, 5 and 7, was able normally to control the reactions of the opposite legs. In two animals the subsequent removal of the entire cortex of the other hemisphere did not affect the reactions of the limbs opposite the remnant.

*Conclusions*—From this study Woolsey and I have concluded that in the monkey the cortical management of those placing reactions which are evoked by tactile stimuli is confined to a zone consisting of the parietal lobe and that portion of the frontal lobe which corresponds to Brodmann's designation of area 4. The cortical motor mechanism essential to the execution of the placing reactions of the limbs of one side is situated in area 4 of the opposite hemisphere. Impulses from tactile receptors in the limbs of both sides and from similar receptors located on both sides of the face can apparently throw this motor mechanism into action, but this effect depends on the integrity of the postcentral gyrus opposite the side stimulated. It is therefore reasonable to conclude that the form of tactile sensibility involved in the elicitation of the placing reactions has a cortical representation which is confined to the postcentral gyrus.

Our results also show that the cortical management of the hopping reactions is situated entirely precentrally and that these responses are independent of all cortical tissue lying outside the frontal lobe. But, as has already been mentioned, they do not permit us unqualifiedly to assert that this cortical mechanism contains a sensory component. That an efferent projection system originating in area 4 is almost completely essential for the occurrence of hopping in the monkey cannot be doubted. The question whether its influence on hopping is exerted through a tonic action on some subcortical center or is the result of its activation by corticopetal impulses originating in proprioceptors is one which cannot be answered by the results of our ablation experiments.

## II THE REPRESENTATION OF TACTILE SENSIBILITY IN THE CORTX OF THE MONKEY AS INDICATED BY CORTICAL POTENTIALS

As already related, the work which Woolsey and I carried out on the central control of the hopping reactions yielded no certain proof that the proprioceptive impulses which induce these responses actually reach

the cortex. About the time that we came to realize this fact we had the good fortune to join forces with Wade Marshall, who, a short time before, had introduced amplifiers and a cathode ray oscillograph into the Johns Hopkins laboratory and had brought with him not only technical competency but also a number of sound and helpful ideas. Together the three of us set out to determine whether a study of evoked cortical potentials might not throw further light on the cortical representation of somatic sensibility. Although we began with the hope that we might settle the question whether touch and muscle sense have topographically separate cortical representations, we were soon diverted by the discovery that our method was capable of revealing in profuse detail a cortical representation of tactile sensibility. For over a year the study of this has constituted the greater part of our joint efforts and only recently have we made rather desultory attempts to solve the original problem. It must be admitted that to date those of our results which bear on the question of the cortical representation of muscle proprioceptors are inconclusive. Consequently, the remainder of this lecture will deal with our more extensive and far more decisive study of the touch representation.<sup>19</sup>

At the time that we began our investigations there had appeared in the literature evidence to show that stimulation of afferent fibers in somatic nerves may induce electrical changes in one or another part of the cerebral cortex and a few observations had indicated that similar cortical responses can be elicited by stimulation of receptors mediating cutaneous or deep sensibility.<sup>20, 21, 22, 23</sup> No one, however, had undertaken a systematic study in which the relationship between the time and place of *both* the peripheral stimulus and the cortical response was rigidly controlled. With arrangements for recording which left no doubt as to whether there was or was not a definite correlation between stimulus and response it was found, first in cats and later in a series of twenty-five monkeys, that the application of discrete tactile stimuli to any cutaneous area produces in the cortex of the anesthetized animal well-localized surface positive waves. These potentials are of such magnitude, show such regularity over long periods of time, and are so decisive in their characteristics that they can be studied with a facility comparable to that enjoyed in studies of the axon potentials of isolated nerve trunks. That our efforts were productive of definite results from the very beginning was, I am sure, largely due to Marshall's insistence upon the use of mechanically discrete stimuli which were brief in duration, low in fre-

quency and near the human threshold in intensity. Thus were avoided the complications attending spatial and temporal dispersion of afferent impulses. Further, this mode of stimulation is strictly physiological, for the impulses which reach the cortex arise in normal fashion from receptors. When a peripheral nerve trunk is stimulated it is no simple matter to make certain that the sensory fibers excited are ones which mediate a single modality, and even if this difficulty be satisfactorily overcome, some doubt must remain whether the centripetal impulses reach the cortex in a pattern which resembles the normal.

*Experimental Methods*—A brief description of the actual experimental procedure used will give a basis for judging the nature and significance of the results obtained. The animals were anesthetized with pentobarbital sodium (occasionally chloralosan or dial was used). After opening the skull and dura so as to lay bare the greater portion of the external surfaces of one or both cerebral hemispheres the head of the animal was placed in a Horsley-Clarke instrument constructed to carry two electrodes. This arrangement permitted rapid and precise placing of the leads on the pial surface. Exploration of one or the other bank of the central sulcus was carried out after the opposing gyrus (precentral or postcentral) had been carefully dissected away. The medial surface of the cortex was exposed for study by removal of the inner portion of the opposite hemisphere. When this had been done one bank of the sulcus cinguli could be explored after careful removal of the other. The electrodes were made of No. 50 cotton thread drawn through steel tubing and kept wet with Ringer's solution. One electrode was placed at a given point on the somesthetic area, the other on an indifferent region, e.g., occipital cortex. Provided such leads are separated by a distance of one centimeter or more, the position of the "indifferent" electrode has no significant effect on potentials attributable to activity under the other. For observing and recording these changes a capacity-coupled amplifier having time constants of 93 and 500 msec. was used in conjunction with a cathode ray oscillograph equipped with a fluorescent screen of medium persistence. It was found that if the animal's blood temperature was maintained at a normal level and if the portions of the exposed pial surface not under exploration at the moment were covered with cellophane the cortex remained in excellent condition for many hours. Each mapping experiment necessarily consumed from twelve to thirty-six hours, and we have uniformly found that during these long periods the potentials

obtained do not progressively undergo significant reduction or changes in character. In the course of some experiments they occasionally diminished in size or even disappeared for brief periods but reappeared and soon gained their previous magnitude.

Stimulation was applied to hair-covered areas by a small camel's hair brush, to bare regions by the tip of a small von Frey hair or a cat's vibrissa. These objects were mounted on a lever rigidly attached to the moving armature of an electromagnetic device the coils of which were energized by a pulse 3 msec in duration. This produced a regular, quick, to-and-fro movement which, at the end of the lever, amounted to a displacement of approximately 0.5 mm within a few milliseconds. Arrangements were such that the movement of the stimulator occurred at a given and adjustable point on the  $x$ -axis line of the cathode ray tube. Thus a clear signaling of the exact time of stimulation was assured. It was found that the application of the stimulator to the skin of a human subject gave a sensation of very light touch which was just above the threshold.

*Characteristics of the Evoked Cortical Potentials*—With the active electrode on a cortical spot corresponding to the peripheral area stimulated a distinct surface-positive wave follows each restricted tactile stimulus. Even when "spontaneous" cortical waves interfere with the simplicity of the record the procedure described above usually enables one to determine the presence or absence of a correlated response. Nevertheless, the "spontaneous" activity does make this determination difficult, and we have therefore ordinarily worked at a depth of anesthesia which gives a reasonably quiet base line, but does not seriously reduce the magnitude of the induced response. Under these conditions the amplitude of a maximal potential usually lies between 100 and 300 microvolts. The rising phase occupies from 3 to 6 msec, the falling phase from 10 to 80 msec. In the monkey the latencies, in milliseconds, average 15 to 20 for toes, 8 to 11 for fingers, and 5 to 9 for face. These values may fluctuate as much as 20 per cent, but are usually constant within 5 per cent.

We have routinely employed a stimulation frequency of not more than one a second. The discrete surface positive type of response with which we are dealing decreases in magnitude as the frequency is increased and it disappears at rates of from 12 to 15 a second. This effect is apparently related to an interesting masking phenomenon which we have encountered. It can readily be shown that a given cortical spot may yield potentials of approximately equal sizes when a discrete tactile stimulus

is applied successively to different points on a restricted peripheral area. Thus brush stimulation of a few hairs within an area on the arm one inch wide and two or three inches long will evoke potentials from a specific spot. These potentials, however, are attenuated or obliterated if another camel's hair brush is applied with a continuous motion anywhere else within that particular skin area. If the secondary stimulation is applied beyond the boundaries of an area represented at the cortical spot it has no such masking effect.

The extinction of the potentials when relatively low frequencies of stimulation are used suggests the development of a long refractory period somewhere in the central mechanisms which respond. Recently Marshall<sup>24</sup> has investigated this phenomenon. In a series of experiments on cats under deep pentobarbital sodium or dial anesthesia one electrode was placed in the lemniscus, a second in the thalamic radiations and a third on the sensory foreleg area of the cortex. The absolute and relative refractory periods (A R P and R R P) were then determined in terms of the potential responses at each electrode to pairs of tactile or light electrical stimuli applied to the contralateral forefoot. The A R P for the lemniscus was found to be less than 5 msec while the second response dropped out in the radiations and the cortex at stimulation intervals as long as 50-60 msec and here the R R P was found to be more than 200 msec. In a second group of experiments on monkeys the cortical responses to weak electrical stimulations of a digit were studied first with the animal under deep ether, then after complete emergence from the anesthetic and finally under deep pentobarbital sodium anesthesia. Multiple electrodes mounted in trephine holes served as leads. With deep ether the A R P is approximately 16 msec, the R R P 72 msec. In the absence of anesthesia the A R P is only 4 msec and the R R P is about 17 msec. But when administration of pentobarbital sodium has resulted in full surgical anesthesia the A R P becomes approximately 38 msec and the R R P occupies an interval of 500-700 msec. These two groups of findings suggest that anesthesia, especially barbiturate anesthesia, tends to block ascending impulses by prolonging the refractory period of thalamocortical neurons. Depths of anesthesia which nearly abolish the spontaneous waves do not significantly affect the amplitude or the latency of the first of a series of evoked responses. A very deep anesthesia, however, does markedly reduce the amplitude.

Restricted tactile stimulation of a specific peripheral locus elicits

responses over a cortical area of several square millimeters, but one or more spots of maximal potential are always found. The site or sites of these can be determined only by moving the electrode in steps of a fraction of a millimeter. The size of the cortical area varies with the part of the body surface at which the stimulus is applied. Stimulation within a region of relatively low sensibility, such as the back, gives rise to potentials which are limited to a very small cortical area. In this case the maximally active spot may be no larger than the effective area of the electrode and it is not uncommon to find that the potential drops to 5 or 10 per cent of maximum when the lead is moved only 0.5 mm. In general the potential decreases somewhat less abruptly in certain directions than in others. When the cutaneous area stimulated is one where tactile sensibility is acute, e.g., the skin of the thumb, the potentials appear over a different but very much larger fraction of the cortical somesthetic area. Further, wherever this is the case, there are two or more spots of major potential situated along a more or less definite strip of cortex. Although the potentials at these spots may be of nearly equal sizes there is usually one which shows a shorter latency than the others, at the other spots the longer latency appears as a 2 to 5 msec shift in the entire wave. The fact that in any cortical area the potentials decrease much more precipitously when the electrode is moved in one direction than in another indicates the part played by purely physical spread. In general our experience suggests that within any area potentials greater than 10 per cent of the maximal are physiologically significant if they occur at distances greater than 1 mm from the maximal point.

At present little can be said concerning the origin of these evoked cortical potentials. The application of Dusser de Barenne's<sup>27</sup> method of thermocoagulation indicates that at least the outer layers of the cortex are not essentially concerned in their elaboration. It is possible that they represent the summed action potentials of the terminations of thalamo-cortical neurons. On the other hand, they may arise in the somata of cortical neurons. The solution of this fundamental question must await the securing of data more pertinent to it than any at present available.

*The Topography of the Cortical Representation*—A general mapping of the entire Rolandic region of one hemisphere can be achieved in a single experiment on a monkey by exploring the entire body surface with the stimulator each time the active electrode is placed on one of a series of arbitrarily selected points. This, however, requires a very long period

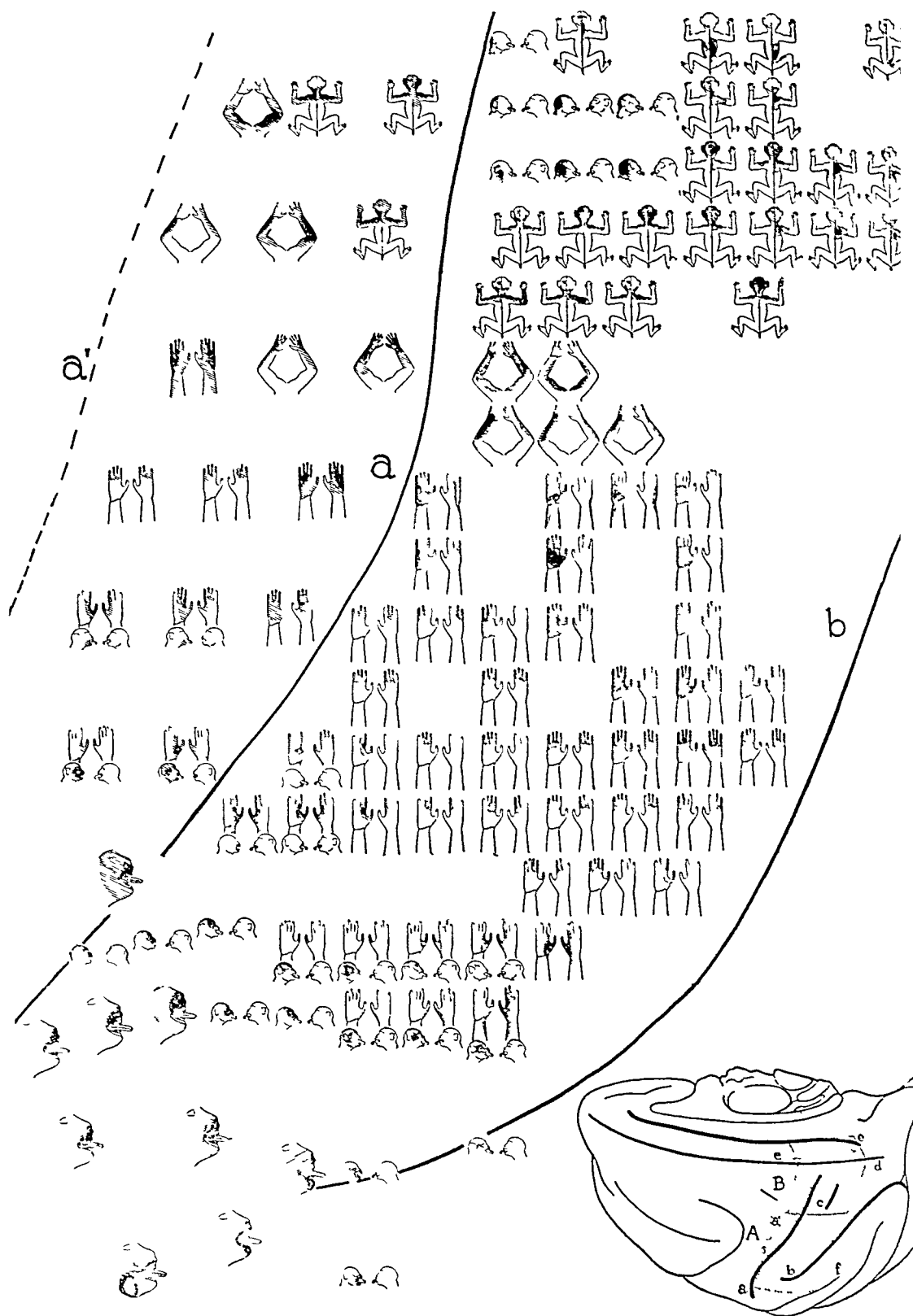


Fig 4 A

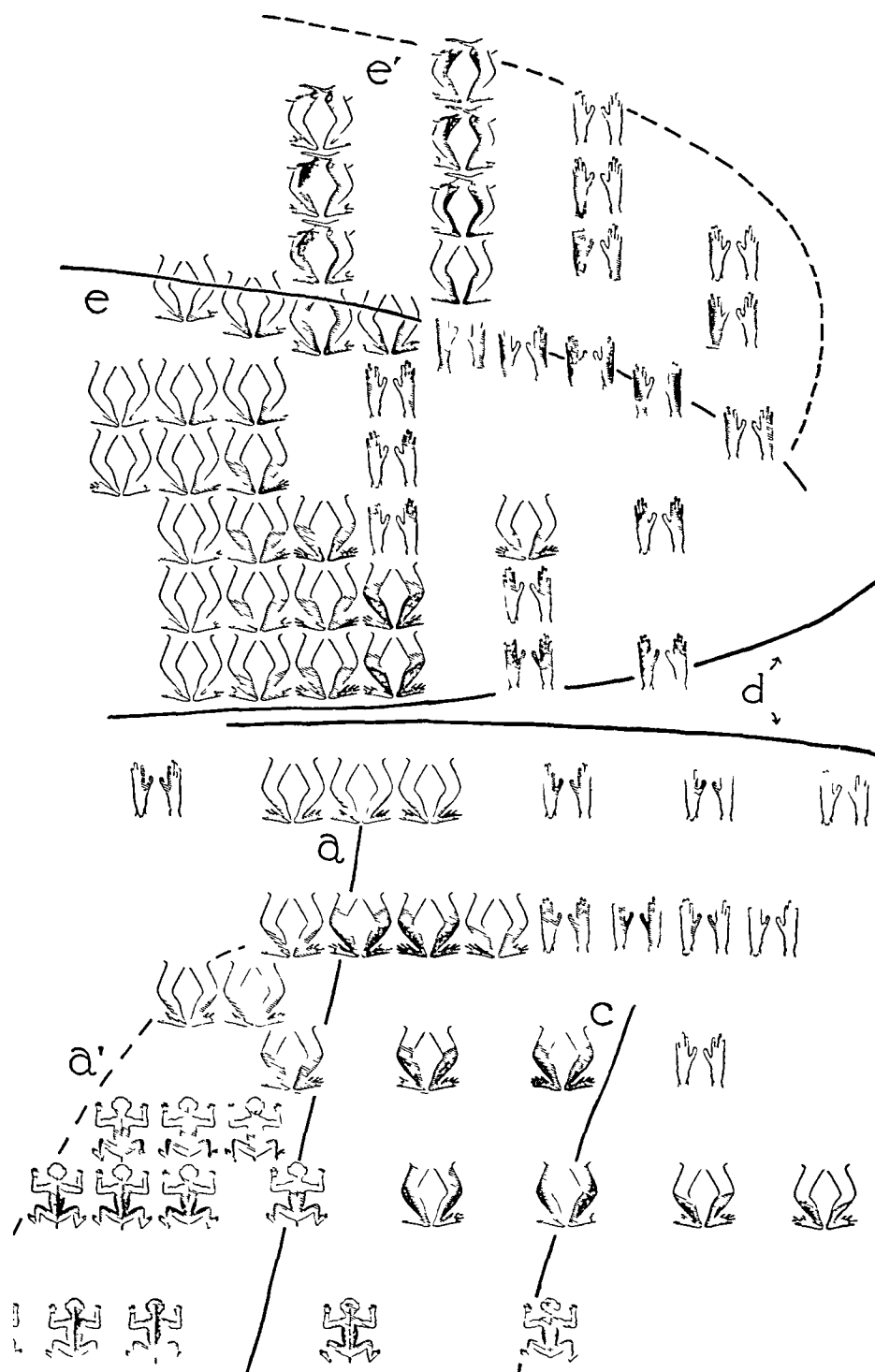


Fig 4 B

experiments a brief pressure stimulus (given by applying the lever-arm of the stimulator to a part) evoked rather weak potentials in the somesthetic area of the ipsilateral cortex, but in these cases it was never certain that vibrations set up by the stimulus were not transmitted to the opposite side of the body where they might easily act as adequate tactile stimuli. No maximal potentials in response to tactile stimulation were ever found precentrally. On following a longitudinal coordinate forward small waves were usually picked up from points just anterior to the central sulcus, but these are probably the result of physical spread from the most anterior parts of the postcentral gyrus. They were never encountered in animals from which the adjacent portion of the postcentral gyrus had been extirpated some time previously.

Inspection of Fig. 4 shows that the representation of each part tends to occupy a narrow strip of cortex which runs diagonally to the sagittal plane. These "diagonals" extend in a posterolateral direction from the central sulcus. Up the postcentral gyrus to the hemispherical rim and then down the medial surface and on to the upper bank of the sulcus cinguli the parts of the contralateral body surface are represented in an orderly sequence. For all portions of the body caudal to the arms the cortical sequence clearly reflects the metameric origin of the dermatomes. This is especially striking in the case of the leg, where the preaxial (dorsal) surface is represented, from hip to hallux, on the dorsal aspect of the hemisphere, while the postaxial (ventral) surface, including the remaining digits, is represented, from toes to hip, on the medial aspect of the hemisphere above the points for perineum and tail. The order is that of the sensory spinal skin-fields as determined by Sherrington<sup>26</sup> for the hindlimb of the monkey. The sequence—hip, leg, foot, toes—shown in charts derived from the results of direct electrical stimulation of the human sensory cortex<sup>5,6</sup> is, in the light of the work with cortical potentials, a limited and only partly correct one. This defect is of course chiefly due to the difficulties which attend exploration of the medial cortical surface during neurosurgical procedures on man. A feature of the sequence disclosed by the evoked potentials which was unexpected and appears to be new is that the head, as well as the neck, is represented between the areas for arm and body. In this region even the face appears to have some slight representation. The face area proper, however, is situated near the lower (lateral) extremity of the postcentral sensory zone.

Before the representation of tactile sensibility had been mapped by the method of cortical potentials Woolsey and I made some attempts to abolish, by means of limited postcentral ablations, the possibility of eliciting placing in response to tactile stimulation of a hand or a foot. After these operations some of the animals showed what might be called "recovery of function." As a matter of fact we lacked at that time any precise criterion of the sensory areas for hand or foot, we could only proceed on the assumption that they were situated directly across the central sulcus from the corresponding motor points. We were of course unaware of the diagonal arrangement of the representation of a part. It can be said, however, that subsequent reference to the maps has indicated that in every case of partial "recovery" the postcentral ablation had been incomplete. More recently we have been able to correlate in one and the same animal the sensory loss determined by a study of the contact placing reactions with that indicated by the method of exploring the cortex for evoked potentials. The results obtained in one monkey are especially instructive. In this animal a segment of the postcentral gyrus lying just above the end of the intraparietal sulcus was removed. Throughout a postoperative period of several months the contralateral hand was regularly placed when the thumb was brought into light contact with the edge of a table, but no placing occurred when this same tactile stimulus was applied to the ulnar side of the hand or to the forearm. Before sacrificing the animal its cortex was examined for potentials in response to tactile stimuli. It was found that the ablation had spared a large fraction of the thumb area, but had almost completely removed the representation of the tactile sensibility of the rest of the upper extremity.

*Discussion and Conclusion*—It must be recognized that in all probability this method does not reveal the entire cortical representation of tactile sensibility. It seems likely that the area within which the evoked potentials have been found is that which receives those thalamocortical fibers which convey impulses originating in tactile receptors. In other words, it is a sensory projection area. Whether the projections from the thalamus to parts of the cortex other than areas 3, 1 and 2 are concerned with tactile sensibility is a question which cannot at present be answered conclusively. It may be pointed out, however, that the anatomical studies of Walker<sup>3</sup> suggest that the part of the thalamus which receives the majority of the fibers of the medial fillet and spinothalamic tracts projects almost entirely upon the cortex of the central sulcus and the postcentral gyrus.

In any consideration of our results the question of the effects of the anesthesia must be given attention. Anesthesia doubtless represses spread of impulses through the cortex and possibly it differentially blocks the entry of tactile impulses into the ipsilateral cortex. In a number of experiments in which several multiple electrodes were mounted in the skull, thus making it possible to record the potentials in the animal after emergence from the anesthetic, evidence has been secured that the anesthetics used do not significantly modify either the form or the locus of the potentials evoked by tactile stimulation. In these experiments without anesthesia we have been unable to demonstrate an ipsilateral representation of the tactile sensibility of the body.

In conclusion it may be stated that this study, based on receptor stimulation and correlated electrical response, has shown that the tactile sensibility of each part of the body is represented in profuse topographical detail over the postcentral gyrus. It does not follow that the total cortical response to a tactile stimulus is confined to this area. It is reasonable to suppose, however, that whatever that response may be it is based on the highly stable anatomical substratum which has been functionally demonstrated in terms of evoked cortical potentials.

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## THE PRESENT STATUS OF GYNECOLOGIC ENDOCRINE THERAPY

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G YNECOLOGIC endocrine therapy has enjoyed an extraordinary development in the last few years. It is only a decade since the only available endocrine products from the ovary or anterior pituitary were desiccated extracts, now regarded as quite inert, but which the gynecologist optimistically made use of. Since then, glandular preparations of three or four major types, each in several forms with varying indications, have become available. Yet it is almost universally recognized that the rapid expansion in the clinical use of these substances has been accomplished at some sacrifice of soundness and sincerity.

The reasons for the vogue which endocrine therapy is enjoying are not hard to find. First, there is the undoubted need for a scientific therapy of the many functional disorders of the female reproductive system. Furthermore, the so-called sex hormones are apparently relatively safe, more or less regardless of dosage, and no accidents have occurred, such as attended the introduction of insulin, thyroid extract or pituitrin. That a certain artificial demand has been created by an advertising campaign to the physician is also probable.

Yet the most important reason for the acceptance of the new products is the brilliance of the basic scientific work which preceded their appearance in the clinical field, for whatever may be said against the new endocrine therapy, it can never be said that it is entirely empirical. The soundness of the reasoning which leads to the prescription of certain gland products is often so good as to make the physician biased in the evaluation of his results. To this sound physiologic background must be added the helpful but misleading fact that gynecologic endocrine dysfunction has a great tendency to spontaneous improvement. A series of optimistic reports has, as a result, led to a rapid approval of the endocrines for many conditions for which more critical judgment may eventually question their value. Any attempt at present to delimit the field of gynecologic endocrine therapy is bound to be tentative and to lead to conclusions which will be unacceptable to many. Nevertheless

such provisional accounting may occasionally be useful

In the following pages, the subject of gynecologic endocrine therapy will be considered under the following heads

(1) The endocrine agents now available for affecting the female pelvic function and their physiologic action

(2) The diagnostic methods available to determine the physiologic nature of the disturbance underlying the patient's clinical symptoms

(3) A classification of the conditions for which the so-called sex hormones have been advised into categories of relatively proven usefulness

## I THE AVAILABLE AGENTS

The agents available for affecting the endocrine status of the female reproductive tract fall into several groups. First are those which in a measure reproduce the function of the ovary itself by acting upon the secondary organs, the uterus, vagina and breasts. This group includes the various estrogenic substances and the specific hormone of the corpus luteum. Second are the substances which affect the ovary and are therefore classed as gonadotropic. They are a somewhat miscellaneous group, both as regards their origin and action. Third, there is the hormone of the thyroid gland whose action on the pelvis is not definitely understood, but whose clinical effectiveness for some conditions seems established. Finally, there is radiation therapy, which as a rule has the opposite action from that of most of the hormones, namely, to reduce rather than increase function.

### A THE ESTROGENIC HORMONE

Estrogenic substances are available for therapeutic use in several forms. The substance most widely employed is probably estrone or ketohydroxyestrin, known to the profession by the terms theelin, folliculin, amniotin, menformon and others. A closely related substance is estriol or trihydroxyestrin, sometimes called theelol. This latter product is somewhat less active than estrone, but has been believed to be more efficient as a preparation to be given orally. A material intermediate in chemical formula between estrone and estriol is estradiol or dihydroxyestrin. This substance has been combined with benzoic acid to form estradiol benzoate, marketed under the commercial names, progynon B or oestroform B. This compound has the property of being more slowly broken up in the body than are the simpler estrogens and has there-

fore the advantage of a more prolonged effect. A fourth estrogenic substance is the one commonly known as emmenin (Collip<sup>1</sup>), and thought to be estriol in a combined form, probably estriol glucuronide (Cohen<sup>2</sup>). It is much less active than are the "free estrogens", perhaps especially in the absence of an ovary, the site of its supposed transformation to a more potent form. It is recommended, however, as a substance especially available for oral administration.

Great confusion has resulted from the fact that the clinician has been subject to a constantly changing nomenclature of dosage, namely mouse units, rat units, and now, unexpectedly, international units. The present unit, accepted by a committee of the League of Nations, is perhaps relatively permanent. This "international unit" is the equivalent of one ten-thousandth of a milligram (0.1 gamma) of a crystalline preparation of estrone. The relation of the animal units to this gravimetric unit is actually quite variable, depending on the method of bio-assay, but a mouse unit is usually accepted as about equal to one international unit, a rat unit to five international units.

Although the use of estrogenic substance has a certain rationale, the dosage for most of its indications is largely empirical. This is obvious when it is remembered that except in the case of the menopause, the degree of ovarian deficiency which must be compensated for by therapy, is unknown. A start toward the development of a rational dosage has been made chiefly in reference to the menopause. Kaufmann<sup>3</sup> in 1932 showed that artificial menstruation could be produced by a dosage of 210,000 mouse units of progynon benzoate followed by 35 rabbit units of corpus luteum. This is apparently the basic requirement for the building up of an endometrium sufficient to cause bleeding. Such a result, however, is unnecessary in usual therapy and the goal is more generally simply the suppression of the excessive anterior pituitary activity which is associated with hot flashes. Frank, Goldberger and Salmon<sup>4</sup> have reported the disappearance of the gonadotropic factor from the urine, the alteration of the vaginal spreads and the disappearance of menopause symptoms when 4,000 rat units are given every other day for two weeks. Thus their figure for the suppression of gonadotropic activity in a woman without ovarian tissue is 120,000 international units of estradiol benzoate in two weeks time. Papanicolaou and Shorr<sup>5</sup> had found that it took from 250 to 300 rat units daily to induce complete changes in the vaginal smear, and with oral administration fifteen to twenty times this dose

Other workers (Werner<sup>6</sup>) have, however, placed the figures somewhat lower and have noted stimulation of the breasts, endometrium and vagina with as little as 5,000 to 10,000 international units. Using a different method of study, that of following urinary excretion of the estrogens, Mazer and Israel<sup>7</sup> noted that an injection of 1,000 rat units in castrated women produced normal levels for four days. Larger amounts, such as 5,000 to 10,000 rat units, produced a temporary hyperestrinism which fell to a normal level by the fourth to fifth day.

The use of estrogenic substance for any purpose in women who have sufficient ovarian function to menstruate does not give dependable results. Since the basic ovarian function which the menstruating patient possesses is difficult or impossible to gauge, the additional estrogenic substance which must be added to raise the theoretically low level to a theoretical normal is the purest guess work.

The functions of the estrogenic hormone which are invoked to support its use in therapy are briefly the following:

(1) To stimulate proliferation of the mucosa of the uterus, vagina and mammary glands and to a certain extent the muscular walls and supporting stroma of these organs. This function is the basis of the treatment of amenorrhea and hypomenorrhea due to deficient development of the endometrium, of dysmenorrhea supposedly due to deficiency of the myometrium, and of senile and juvenile vaginitis.

(2) To increase the sensitivity of the uterine musculature. This function has given rise to little definite therapy, although the estrogens have been suggested in the therapy of missed abortion and postmaturity in obstetrics.

(3) To suppress excessive activity of the anterior pituitary gland. Continuous small doses of estrin have apparently found a definite place in the therapy of the menopause. A somewhat paradoxical effect may, however, be produced when very large doses of an estrogen are given and, instead of a suppression, a temporary increase in gonadotropic activity, especially in its luteinizing function, may result. This reaction may be at the basis of successful therapy of amenorrhea with large doses of estrin.

The dangers of estrogen therapy are, like its uses, somewhat theoretical. The experience of research in mammary gland cancer in mice, where the ovarian hormone undoubtedly is a factor in bringing out latent tendencies to cancer in susceptible strains, leads to some anxiety

as to the effects of the too indiscriminate use of this agent Mammary carcinoma developing during or after estrogen therapy is sometimes heard of, but such a coincidence must of necessity occasionally occur in view of the frequency of spontaneous breast cancer Depression of the pituitary, and indirectly of the ovary, by long-continued injections is theoretically possible (Clauberg and Breipohl<sup>8</sup>) Immediate reactions associated with swelling of hands, face and eyes have been noted (Klaften<sup>9</sup>) and unexpected uterine bleeding is not unusual

#### B CORPUS LUTEUM HORMONE

Desiccated tablets of corpus luteum gland have been in use for a long time, but it is only a few years since active preparations have been available The names under which the hormone passes include progestin, progesterone, corporin, proluton, lipolutein and many others

The question of units is again a confusing one Two biologic units have been tried, one based on the use of an adult, the other on an immature female rabbit The former gives the American or Corner-Allen unit, which is about twice the size of the Clauberg or European unit (Young<sup>10</sup>) More recently an international unit has been introduced, which is the equivalent of one milligram of pure crystalline progesterone This unit is a little larger than the Clauberg rabbit unit, considerably smaller than the Corner-Allen unit It is well to remember that an international unit of corpus luteum is one milligram, an international unit of estrone one ten-thousandth of a milligram, for otherwise the respective doses of the two substances seem completely out of harmony

The dosage of corpus luteum hormone is again largely empirical In castrated women Kaufmann<sup>3</sup> found that from 35 to 90 rabbit units (Clauberg) needed to be added to change a proliferative phase produced by estrogenic substance to a truly secretory endometrium On the other hand clinical results have been reported in dysmenorrhea with dosages varying from 2/25 to one rabbit unit

The functions of the corpus luteum hormone upon which therapy is based are the following

(1) The transformation of a proliferative to a secretory type of endometrium This effect leads to the use of the hormone in cases of bleeding due to a hyperplasia of the endometrium, and perhaps also in sterility when theoretically due to a deficient corpus luteum preparation of the endometrium

(2) The control of nidation of the ovum This function is bound up with the one just mentioned, for the protective effect of the corpus luteum on early pregnancy is in all likelihood the stimulation of early decidual development The loss of the corpus luteum early in pregnancy is well known to result in abortion, and the hormone has accordingly been given in threatened or habitual abortion on the theory that a natural deficiency in the patient is to be remedied

(3) Reductions in sensitivity of uterine musculature Repeated observations and experiments have indicated that under the influence of progesterin the uterine musculature becomes less responsive to certain stimuli, such as pituitrin, and that the uterus of certain animals is less active during times when corpora lutea are present In this respect the effect of progesterin is antagonistic to that of estrin This function has been used to build up a corpus luteum therapy of dysmenorrhea The same rationale can be found for its use in after pains following labor

In general, progesterin has been available until very recently in amounts too small for its wide trial in physiologically effective doses No deleterious effects are yet recognized, beyond possibly a disturbance in menstrual rhythm or in the amount of flow

#### C THE GONADOTROPIC HORMONES

There are certainly several substances which affect the ovary and the testis and it is of primary importance to recognize the essential differences in their actions Two effects on the ovary are of possible clinical importance, the stimulation of follicle growth itself and the luteinization of follicles already present The former function is, in general, predominant in substances derived from the urine of women in the menopause and from the pituitary gland itself, the latter in products derived from the urine of pregnancy and from the placenta

(1) The true anterior pituitary hormone is essentially follicle-stimulating This or related substances have been variously styled FSH (follicle-stimulating hormone), maturity factor, prephysin and gonadogen and prolan A Even substances within this group undoubtedly differ from each other in their physiologic effects, depending upon their source

The units of measurement of the follicle-stimulating hormone depend upon the production of mature follicles in the ovary of an infantile rat or mouse or upon an accepted percentage increase in the weight of the ovary or of the uterus The clinical dosage is quite undetermined, and

it is possible on account of the scarcity and expense of the material that practically all recommended or reported doses have been insufficient to produce true clinical effects

The use of the follicle-stimulating hormone is based on its known effect in causing development of the ovary and follicle formation. On account of this it may logically be used in any condition of known hypovarianism and its secondary genital underdevelopment. It is perhaps especially indicated in sterility due to failure of normal ovulation.

(2) The gonadotropic substances derived from pregnancy urine have been called APL (anterior-pituitary-like), prolan B, antuitrin S, antophysin and follutein. The standard on which this substance is measured is based upon the production of corpora lutea in immature rats or sometimes in mice.

The dosage here is again still on an empirical basis but the supply of this hormone is sufficiently great to have permitted the trial of a wide range of dosage. Novak and Hurd<sup>11</sup> reported success with 200 rat units daily in cases of functional bleeding. Kurzrok<sup>12</sup> advises 750 rat units daily in cases of severe bleeding. On the other hand, Hamblen<sup>13</sup> failed to find evidence from endometrial biopsy that ovulation or corpus luteum formation had occurred after total doses of 6,000 to 24,250 rat units in daily amounts of 400 to 8,000 units.

On account of its known luteinizing effect on the immature ovaries of mice, the luteinizing hormone is recommended clinically whenever the corpus luteum is theoretically deficient. Thus it is advised especially in cases of dysmenorrhea and functional uterine bleeding. For the latter, a direct effect on the endometrium itself has also been claimed. The substance is likewise used, although probably without a sound theoretical basis, for various types of ovarian underfunction.

(3) A third hormone of the anterior pituitary is thought to stimulate secretion of the mammary gland. The substance is measured in so-called bird units, depending upon its effect on the crop glands of pigeons. It has been available as prolactin and has been used to stimulate the secretion of milk in the postpartum period (Kurzrok, Bates, Riddle and Miller<sup>14</sup>) and in chronic mastitis (Lewis and Geschickter<sup>15</sup>).

The dangers of the use of the gonadotropic substances are not known, and are probably not great. On account of the fact that these are complex molecules and are not yet available as pure products, local and general reactions sometimes occur. The luteinizing substance is not be-

lieved to have a simple physiologic effect on human ovaries, and abnormal cystic follicles may be produced (Geist<sup>16</sup>) Certain defects produced in the offspring of mice injected with this material have led at least two observers to suggest that anterior pituitary hormone should not be given during the child-bearing period (Wolff<sup>17</sup>) The contraindications based on animal experimentation have probably about the validity of indications on the same basis

#### D RADIATION OF THE OVARY

It is perhaps unconventional to include radiation under the heading of endocrine therapy, but this is actually a most precise and effective method of influencing ovarian function The small dosage of radiation usually employed in gynecologic work shows that it is the ovarian effect which is depended upon in practically all indications, except in the control of malignant tumors

It is possible to produce certain different effects upon the ovary by varying the radiation dosage A large dose will permanently suppress the ovarian function by destroying all the follicles, while one which is somewhat smaller, 28 per cent of a skin erythema according to Wintz<sup>18</sup>, will cause a temporary amenorrhea by injuring only those approaching maturity That a still smaller dose has a "stimulating" effect is a possibility raised by certain reported successes in the treatment of amenorrhea and sterility

The disadvantages of radiation therapy are well known The disappearance of the original symptoms almost always coincides with the appearance of the symptoms of the menopause Where a temporary amenorrhea is attempted, the chance of it becoming permanent must be accepted The possibility of damage to the germ plasm, on the other hand, must be thought of when conception occurs after a temporary amenorrhea In spite of these objections the place of radiation of the pelvis in the endocrinologic field is assured The invariable control of functional uterine bleeding in women approaching the menopause is alone a more brilliant endocrine success than anything attained by the injection of hormone substances

Radiation of the pituitary either to diminish or stimulate function has a much less recognized position The doubt which usually exists as to the actual relationship of the pituitary to the symptoms, the uncertainty as to dosage, the unknown effect on brain structure, and the not

infrequent loss of hair, combine to make this an unacceptable procedure except in research clinics

#### E THYROID EXTRACT

Thyroid extract must be mentioned in any list of endocrine agents affecting the pelvis. The exact nature of its action on the genital organs is unknown, but the clinical fact of disturbances in the reproductive functions in association with thyroid disease is well established. The frequent reports of thyroid extract successfully used to control pelvic dysfunction, especially in patients who have a low basal metabolism or who are overweight, demands its early consideration in all such cases.

### II DIAGNOSTIC PROCEDURE IN GYNECOLOGIC ENDOCRINE THERAPY

It would be an enormous aid to intelligent therapy if there were satisfactory means of measuring the activity of the ovary and pituitary gland and actually determining the type and degree of dysfunction from which a patient with given symptoms is suffering. Actually, although such terms as "hypopituitarism" and "hyperestrinism" are rather commonly used, they are based largely upon supposition.

Certain tests to measure the function of the ovary and anterior pituitary have, it is true, been in use for some time and are constantly being improved. They represent a thoroughly sound approach to the problem, but one which has as yet limited practical applications. The tests are apt to be overlooked by the majority and perhaps overestimated by the remainder of the profession. A simple attention to details of the history and physical examination will in many cases give as much information as can be obtained. Under certain circumstances, however, a few additional procedures may be of great value.

#### A THE HISTORY

Here the patient's age, the evidence of fertility as derived from the dates of her pregnancies and the use of contraceptives, as well as changes in weight, are of fundamental importance. The menstrual history, however, deserves the greatest consideration. It is well to remember that the changes in the timing of the periods must always be ascribed to a deviation from the normal ovarian function in the form of delays or accelerations of the development of the follicle or corpus luteum. Changes in the amount and duration of the flow, especially if this be in

the form of an increase, are much more apt to be due to local causes in the uterus than to a glandular disturbance

#### B THE PHYSICAL EXAMINATION

The physical examination is also of obvious value. The state of the patient's nutrition, especially if there has been a recent pronounced increase or decrease in weight, has a great bearing on pelvic glandular function. Peculiar distributions of fat and hair, although written and talked of considerably, appear to be of little importance unless the degree of deviation from the normal is very marked. A rough gauge of the patient's constitutional degree of reproductive development may be obtained from noting the size of the breast and nipples, as well as the external genitalia, vagina, and uterus. In contrast to this, some idea of existent ovarian function may be obtained by noting the degree of congestion or ischemia of the vaginal and cervical mucous membranes. The palpation of the ovaries may be important, especially if enlarged, and hence probably cystic organs are detected.

#### C ENDOMETRIAL BIOPSY

The patient's own endometrium is decidedly the best test object to determine qualitatively, at least, the presence of ovarian and corpus luteum hormones. Fragments of the endometrium are readily obtained without anesthesia by various types of curettes devised for the purpose (Klingler and Burch,<sup>19</sup> Novak,<sup>20</sup> Hoffmann,<sup>21</sup> Rock and Bartlett,<sup>22</sup> Campbell, Lendrum and Sevringhaus<sup>23</sup>). By correlation of histologic sections with the time in the cycle at which the biopsy is taken, the presence and relative durations of the follicular and corpus luteum phases may be determined. The method may be of special value in the classification of amenorrhea and in the detection of a non-ovulatory cycle as the cause of sterility.

#### D VAGINAL SMEARS

It has been shown by Papanicolaou and Shorr<sup>5</sup> that smears of the vagina from women in the menopause are made up of leukocytes and of compact, round or oval cells with well preserved nuclei from the deeper layers of the squamous epithelium. The follicular phase of the menstruating woman and the vaginal secretions of a menopause patient inadequately treated with estrin are characterized by an absence of leuko-

cytes and of the oval nucleated cells, while in their place are found flat, enlarged cells with small pyknotic nuclei. Numerous intermediate types of smears occur, corresponding perhaps to various degrees of vaginal atrophy. The study of the vaginal smears is of some practical use in determining whether an adequate amount of estrin has been given for the treatment of menopause symptoms, and perhaps for the separation of the so-called hyperhormonal amenorrhea from the common type due to ovarian underfunction.

#### E BASAL METABOLISM

A basal metabolism determination is of enormous importance in gynecologic endocrinology. It is one of the few tests which are roughly quantitative, and if abnormal readings are obtained, adequate agents are at hand for their correction. A basal metabolism test is particularly indicated where sterility is present with obesity or abnormal bleeding occurs unassociated with a hyperplastic pattern of the endometrium.

#### F BIO-ASSAY OF ESTROGENIC SUBSTANCE IN THE BLOOD AND URINE

This procedure is one of the most interesting of the methods of clinical study of reproductive physiology. Many clinicians feel that the ultimate has been done for the patient with a genital dysfunction when she is referred for "hormone studies." Few realize that the procedure is still largely in the research stage and that unless the tests are performed with exactness and enormous labor and expense, they are of absolutely no value.

The assay of a single specimen of urine for estrin involves several chemical steps and the use of perhaps twenty castrated mice or rats. It must also be remembered that the excretion of estrin is quite variable throughout the menstrual cycle, and that a report on a single specimen may give a quite erroneous idea of the patient's ovarian function. Even four specimens taken at weekly intervals may accidentally strike only the peaks or the depressions in the irregular curve of estrin excretion. It is scarcely possible to avoid, then, some system of continuous study, such as the assay of consecutive 72-hour specimens, throughout the cycle. Such a routine is confining to the patient and the actual cost of the test to the laboratory cannot be less than a hundred dollars. Tests made upon the blood are even less satisfactory, for a mouse unit is rarely present in less than 40 cc. The amount of blood that would be required

practically precludes repeated tests or a quantitative assay

The indications for such an assay of the estrogenic hormones in practice are at present few. If a patient menstruates, it may be assumed that a definite amount of estrogenic substance is being excreted. Furthermore, enough data have not yet accumulated upon urinary assays to define the range which should be considered normal. Only if very large or very small amounts are excreted can the figure be given much significance. In amenorrhea, the test may be of use in determining prognosis and possibly in avoiding the mistake of treating a rare case of hyperhormonal amenorrhea with estrogenic substance.

#### G BIO-ASSAY OF GONADOTROPIC SUBSTANCE

The study of anterior pituitary hormone excretion is often attempted in association with estrogenic assays. It must be remembered, however, that except during pregnancy and in pronounced degrees of ovarian underfunction, the gonadotropic hormones are present in the urine in amounts too small for accurate measurement. Various workers, it is true, have reported gonadotropic hormone in the urine of normal women especially at or near the time of ovulation (Zondek,<sup>24</sup> Katzman and Doisy,<sup>25</sup> Kurzrok *et al*,<sup>26</sup> Frank and Salmon<sup>27</sup>). The results of different workers have varied so much from each other, however, that the test must be regarded as having as yet little value in routine clinical procedures. Certainly the number of units of gonadotropic hormone reported from a laboratory has no absolute significance, and the validity of the entire report depends entirely upon the accuracy and sincerity of the laboratory doing the assay. The field for the tests for gonadotropic hormone in the non-pregnant woman is certainly at present very small. Possibly it may give an indication of the type and prognosis of certain forms of amenorrhea. Other uses for the test may develop with refinement of methods.

#### H CORPUS LUTEUM

Corpus luteum hormone cannot be detected in the blood or urine of the non-pregnant patient. For this reason, until very recently, the endometrial biopsy taken shortly before menstruation has been the only way of determining whether a corpus luteum has been produced. The recent discovery that corpus luteum was excreted in the form of sodium pregnanediol glucuronide (Venning and Browne<sup>28</sup>), and that this substance could be extracted from the urine and measured, points perhaps

Many reports on this type of therapy have been favorable, both for vaginitis (Davis,<sup>36</sup> Jacoby and Rabbiner<sup>37</sup>) and for vulvitis with pruritus (Rust,<sup>38</sup> Klaften,<sup>9</sup> Wetterwald,<sup>39</sup> Schockaert,<sup>40</sup> Bécèle<sup>41</sup>)

In the treatment of senile vaginitis care should of course be taken to exclude specific organisms, such as the *Trichomonas vaginalis* but after such causes have been excluded, estrogenic therapy appears to offer the best chance of success. As regards dosage, the widest possible range has been recommended. Davis<sup>36</sup> reported success with 100 rat units subcutaneously, three times a week, the average treatment lasting six weeks, and alleviation of symptoms being usually noted in ten days. Several writers recommend doses as high as 50,000 international unit equivalents of estradiol benzoate once or twice a week for periods of two months. Estrin in ointment (Klaften<sup>9</sup>) or a suppository has been given successfully. On the whole, it seems advisable to give a dosage similar to that employed for the vasomotor symptoms of the menopause, beginning with a dose of 10,000 international units twice a week and gradually reducing it, with a reservation of the dose of 50,000 units for the cases of failure with the smaller amount.

B. CONDITIONS FOR WHICH ENDOCRINE AGENTS MAY WITH JUSTIFICATION BE TRIED AFTER OR IN ASSOCIATION WITH OTHER THERAPEUTIC MEASURES

In this group of cases the value of endocrine agents is still a matter of dispute. Custom has somewhat justified their use. Nevertheless, success is not sufficiently consistent, nor is the rationale always clear enough to permit any of the hormones to be termed specific. No practitioner is justified in beginning and ending his therapy with their use, and heavy responsibility rests upon him if he fails to search for other than endocrine causes for the symptoms.

1. *Amenorrhea*

In approaching the therapy of amenorrhea in a younger woman, one must remember that the physiologic basis of the condition is quite different from that of the absent menstruation of the menopause. Complex disturbances in gland relationship, little understood, are present and the simple addition of the ovarian hormone is not necessarily the correct way to relieve the symptoms. Certain diagnostic procedures always must be carried out before sex hormone therapy can be con-

sidered Constitutional disease, particularly tuberculosis, should be excluded and nutritional disturbances with marked abnormalities in weight attended to. Finally, the basal metabolism must be determined and, if abnormal, correct treatment instituted.

If therapy with one of the sex hormones is to be given a trial, a classification of the amenorrhea should be attempted. There are certainly several types: one, with absent or low ovarian function, one, much less common, with a high or normal ovarian function, the so-called polyhormonal amenorrhea (Zondek<sup>24</sup>). The differential diagnosis may perhaps be made by observing the condition of the pelvic mucous membranes, more definitely by endometrial biopsy or assay of the estrogenic or gonadotropic excretion in the urine. Many of these cases are probably instances of a primary pituitary disturbance, so that an anterior pituitary hormone is theoretically indicated. The luteinizing hormone of pregnancy urine is not, however, correct from a physiological standpoint, nor has it given satisfactory results. The follicle-stimulating hormone has perhaps not been given sufficient trial in adequate dosage to have its value known, but failures have been reported (Frank *et al*<sup>42</sup>).

There remains the estrogenic substance which in sufficiently large dosage will often produce some uterine bleeding. Its disadvantage is that usually the only period that occurs is that immediately following a course of therapy. This is to be expected since the drug is essentially substitutional. It is probable, however, that in some cases, 20 per cent according to Mazer and Israel,<sup>7</sup> the menstrual cycle is successfully "started up" after the first period, perhaps through some effect of the massive dosage on the pituitary. An occasional conception has also been reported following such therapy.

The dosage required to produce a menstrual period in an amenorrheic woman is more variable than in a surgical castrate or a woman in the menopause. Rock used an average of 50,000 rat units of "folliculin" and 50 rabbit units of corporin over a three-week period. Mazer and Israel,<sup>7</sup> although reporting a high percentage of temporary successes, had one failure in a patient receiving a total of 675,000 rat units. Frank and his associates<sup>42</sup> using doses from 80,000 to 3,450,000 international units noted no responses below 1,000,000 international units, and a failure was recorded with the highest dose given. It appears clear, as these workers point out, that other factors besides ovarian deficiency are responsible for amenorrhea.

Amenorrhea in itself is probably not harmful and only in an occasional case will it appear justifiable to give injections of estrogenic hormone. When this agent is employed, short courses with relatively high dosage, possibly 50,000 international units every other day for two weeks, should be given with intervals of a week or two of rest in between. Corpus luteum hormone given in doses of one to five units every day for three or four days at the end of the course of estrogenic therapy may serve to make the bleeding, if it occurs, histologically more realistic, but it is questionable whether it contributes anything toward a permanent cure (Elden,<sup>43</sup> Rock<sup>44</sup>). Such treatments, as outlined, are very expensive and the chance of lasting improvement is small.

In most exceptional cases, presumably in those of polyhormonal amenorrhea with cystic ovaries, two other methods of approach may be of help. One is the use of so-called stimulating x-ray to the ovaries, for which considerable success has been reported (Kaplan<sup>45</sup>). The other is a surgical operation with removal of a part of each cystic ovary (Robinson<sup>46</sup>).

## 2 *Abnormal Uterine Bleeding*

A careful exclusion or correction of organic causes of uterine bleeding is essential before any endocrine therapy is to be thought of. Systematic physical examination will disclose the majority of these organic lesions, but the possibilities of an endometrial polyp, submucous fibroid or retained placental fragment, even of endometrial carcinoma, will remain. Before the age of forty the frequency of the last cause is so small as to justify some delay in the performance of a diagnostic curettage, but in older patients the physician accepts considerable responsibility in attempting a hormone therapy without first exploring the uterine cavity.

The plan of treatment adopted for abnormal uterine bleeding will therefore differ markedly according to the patient's age. Before the fortieth year endocrine therapy—thyroid extract in cases with a low basal metabolism or either the luteinizing or the corpus luteum hormone itself—may justifiably be tried. After the age of forty, if bleeding recurs following curettage, the best plan is probably to resort at once to some form of radiation therapy with the aim of suppressing completely the ovarian function. Whether, following curettage, hormone therapy is of value to prevent return of the bleeding, is at present unknown and will

be difficult to prove

The use of the luteinizing hormone of pregnancy urine has already had a number of years of trial. Novak and Hurd<sup>41</sup> in 1931 reported improvement in all but seven of fifty-one cases and recommended a dose of 200 rat units, to be repeated one to six times. Wilson and Kurzrok<sup>47</sup> stated in 1936 that practically every case of functional uterine bleeding could be controlled with pregnancy urine extract if adequate dosage were employed. Their recommended average dose during periods of active bleeding was 200 to 750 rat units daily, followed when the bleeding ceased by 200 rat units once or twice a week for several weeks or months. In contrast to the optimism of these reports is a growing scepticism among many gynecologists, as well as a few definite reports (Keene and Payne<sup>48</sup>, Jeffcoate<sup>49</sup>) which indicate that the brilliant claims of the early investigators are not being substantiated. Opinion is crystallizing that this hormone justifies a trial in bleeding during early and middle life, but that failure frequently follows its use even in these years, and other methods must often be resorted to (Meigs,<sup>50</sup> Smith and Rock<sup>51</sup>).

Corpus luteum hormone has also been advocated for menorrhagia and metrorrhagia (Wilson and Elden,<sup>52</sup> Stemmer,<sup>53</sup> Preissecker<sup>54</sup>) with the object of luteinizing the endometrium which in certain forms of functional bleeding is characterized by a morphology believed to be estrogen-produced. Although Wilson and Elden<sup>52</sup> have written of successes with small fractions of a rabbit unit, such dosages seem inconsistent with the amounts needed to produce a progestational change in the castrate uterus. Few clinical reports are available, but it would appear that if this form of therapy is to be tried, a dose of at least one rabbit unit daily should be given for several days before the expected excessive period is due, or during intervals of abnormal bleeding.

### 3 *Dysmenorrhea*

The theories offered to explain the so-called primary or essential dysmenorrhea are sufficiently varied to furnish grounds for almost any type of endocrine therapy. If the disease is due to the myometrial insufficiency of an underdeveloped uterus, one may with reason recommend an estrogenic substance, while if it is due to a hypersensitivity of the musculature from excessive estrin, then a corpus luteum hormone is to be advised. On the other hand, adherents of a mechanical theory still exist who feel that a dilatation of the cervix or a straightening of the

canal by a stem pessary is the only direct approach to the problem. With the cause of the symptom still unknown, some empirical but systematic plan must be adopted which will start with the simplest measures and work up slowly through the more complicated, in the hope that a means to give relief may be found without the necessity of resort to surgery.

It is again essential that secondary dysmenorrhea due to organic lesions be carefully excluded before the endocrines are thought of. When the pain appears only after several years of normal periods, one must search especially for such conditions as inflammatory disease, a myoma or adenomyoma, or a congested pelvis with uterine malposition.

If no organic basis is found, the next step is to review the possibilities of excessive fatigue, nervous stress, constipation, and other factors capable of affecting the autonomic nerves and the vascular system of the pelvis. An adjustment of the patient's daily activities and the improvement of her general health will yield the largest fraction of the cures to be obtained by the entire list of therapeutic procedures.

If general measures fail, endocrine therapy may be tried, because it is simpler than any form of surgical approach. Two hormones may be considered, estrogenic for the hypoplastic uterus, and corpus luteum for the hypercontractile one (Cannon<sup>55</sup>). Both conditions are admittedly somewhat theoretical entities, especially the latter. In general the patient with a uterus of normal size is most logically treated by progesterone, and with this therapy some successes have been noted (Elden and Wilson,<sup>56</sup> Lackner, Kohn and Soskin,<sup>57</sup> Kotz and Parker<sup>58</sup>). Although smaller doses have been reported as effective, a rabbit unit given every other day during the fourteen days preceding menstruation would appear to be a minimum reasonable dosage. Instead of the corpus luteum itself, the luteinizing factor from pregnancy urine has been advised (Novak and Reynolds,<sup>59</sup> Browne<sup>60</sup>). On the other hand, in patients with very small uteri, estrogenic substance usually administered during the first half of the cycle may be given, either alone or preceding the progesterone injections of the latter half of the month.

It must finally be re-emphasized that no one has yet proved that dysmenorrhea is an endocrine disease, to say nothing of demonstrating the type of glandular dysfunction present. Endocrine therapy of the present types may be counted upon to give frequent failures. The passage of time, marriage and conception are still the factors which determine

the final cure for most women. On account of the occasional necessity for immediate relief, there is still a place for dilatation of the cervix, rarely the suspension of a retroverted uterus, exceptionally perhaps the resection of a presacral nerve.

#### 4 Sterility

An imposing list of diagnostic procedures must be carried out in cases of sterility before a position is reached where hormone therapy is permissible. The male must be examined and the semen studied. Gross lesions in the female pelvis must be excluded, the patency of the tubes determined and any minor infection of the cervix cleared up. The diet should be considered and gross nutritional defects corrected. In the majority of cases a cause for the sterility will be found during these procedures.

If the endocrine field is to be explored, the determination of the basal metabolism is undoubtedly the first step. Cases of hypothyroidism treated with thyroid extract are generally agreed to give the most favorable results in this difficult group. Beyond this is uncertain ground. If the uterus is underdeveloped, relatively small doses of estrogenic substance may be given during the first half of the menstrual cycle over several months time. Kurzrok's<sup>12</sup> recommendation of not more than 75,000 to 100,000 international units, parenterally, or five times that amount by mouth during any one cycle, seems a logical one. In a certain proportion of cases endometrial biopsies, taken shortly before menstruation, may give an indication of the degree of corpus luteum activity and perhaps show the absence of ovulation. In these cases corpus luteum hormone or a follicle-stimulating hormone to induce ovulation may be tried. Finally, when other methods have failed, success may sometimes be obtained by "stimulating" doses of x-ray to the ovaries (Rubin,<sup>61</sup> Kaplan<sup>45</sup>). Even resection of the enlarged cystic ovaries has been recommended, but is not now often resorted to. Surgical procedures should only be undertaken when the patient's desire or need of a child is very great, and she should not be deceived as to the probable chances of success.

#### 5 Habitual and threatened abortion

The causes of abortion are far from understood and it is probable that many are rooted in primary defects of the ova or spermatozoa.

Nevertheless it is tempting to believe that a corpus luteum deficiency, acting either to cause a defective decidua or an overactive myometrium, may play a part in abortion. Providing that other causes are carefully considered, such as hypothyroidism, dietary deficiencies, and organic disease in the pelvis, it is permissible to add corpus luteum as a part of a plan of treatment. Numerous clinical reports are available to indicate its value. Falls, Lackner and Krohn<sup>62</sup> in 1936 reported success in all but seven of forty-one cases of so-called habitual and threatened abortion. They recommended one rabbit unit twice a day in cases of threatened abortion until the symptoms had subsided and in cases of habitual abortion one rabbit unit prophylactically twice each week until the thirty-second week of pregnancy. That Kane<sup>63</sup> in the same year obtained equally good results from treatments with only  $1/25$  of a unit is another example of the uncertainty of dosage with these substances. Furthermore if, as appears probable, the smaller dosage was physiologically insignificant, the series of Kane may serve as a control to show what is to be expected in cases of repeated abortion when they are given simply the best of general attention without specific treatment.

### 6 *Chronic cystic mastitis*

For a number of years certain diseases of the breast, notably that associated with a painful nodularity, have been treated with estrogenic substances. The reported results have been equally good whether the therapy has been by the undoubtedly inert tablets of ovarian residue of 1931 (Cutler<sup>64</sup>) or the potent preparations of 1937 (Lewis and Geschickter<sup>15</sup>). Indeed, with the current belief in the estrogenic *cause* of many breast lesions, to find a rationale for an estrogenic *therapy* requires a dextrous rearranging of the physiologic diagrams of endocrine interrelationships.

The above is a personal opinion and it must at once be conceded that many clinical reports do indicate a favorable effect when estrogenic hormone is given to cases of chronic mastitis. In cases in which the possibility of a malignant neoplasm has been unquestionably excluded and the symptoms are severe enough to merit any therapy, estrogenic hormone may be tried. The plan of therapy advocated by Lewis and Geschickter<sup>15</sup> is to give 10,000 international units at each injection, twice a week for six doses the first month, once a week for three doses the next month, twice the third month, and once during the premenstrual

weeks of the fourth, fifth and sixth months of therapy

In a rare case of marked painful congestion of the breasts in patients near the menopause, radiation of the ovaries will offer a successful means of endocrine therapy. The dramatic relief which follows a reduction in the ovarian function more than compensates for a slightly premature menopause in exceptional cases of this type.

#### IV CONDITIONS FOR WHICH ENDOCRINE AGENTS ARE ON TOO UNTRIED A BASIS FOR GENERAL USE

There is, finally, a long list of conditions for which the sex hormones have occasionally been tried, but for which the conscientious physician should resort to endocrine therapy with considerable hesitation. The conditions placed in this group have been so classed for several reasons. First, the indications may be relatively rare and sufficient cases have not yet accumulated to afford material for adequate trial. Second, the original reports of success may have remained relatively uncorroborated and the silence of other physicians be suggestive of disappointment. Finally, the general nature of the condition, as we now know it, may be such as to make the sex hormones appear too remotely related to promise an effective influence. It is conceded that arguments could easily be brought to transfer certain of the conditions listed in group III to group II and vice versa. Certainly it is probable that the next few years will see many changes in classification. In general, however, a case may be made for the statement that the endocrine treatment of the diseases to be listed in group III has neither the support of proved efficiency, of established rationale, or even of accepted practice.

The conditions which might be placed under group III are too numerous for more than an incomplete list.

##### A ESTROGENIC HORMONE

1 Hypertension (Schaefer,<sup>68</sup> Wallis,<sup>66</sup> Fellner<sup>67</sup>) 2 Involutional melancholia (Schube and associates,<sup>65</sup> Sevringhaus,<sup>69</sup> Werner<sup>70</sup>) 3 Migraine (Glass,<sup>71</sup> Blakie and Hossack,<sup>72</sup> Thomson<sup>73</sup>) 4 Frigidity 5 Epilepsy (Schaefer and Brosius<sup>74</sup>) 6 Eclampsia (Shute<sup>75</sup>) 7 Vomiting of pregnancy (Hawkinson<sup>76</sup>) 8 Postmaturity and missed abortion 9 Uterine inertia (Robinson<sup>77</sup>) 10 Menopausal arthritis 11 Urinary incontinence (Hoffmann<sup>78</sup>) 12 To delay menstruation (Foss<sup>79</sup>) 13 Hemophilia (White,<sup>80</sup> Kimm and Van Allen,<sup>81</sup> Birch<sup>82</sup>) 14 Atrophic

rhinitis (Mortimer, Wright and Collip<sup>83</sup>) 15 The Cushing syndrome (Dunn<sup>84</sup>)

B GONADOTROPIC HORMONE

1 Migraine (Moffat<sup>85</sup>) 2 Acne vulgaris (Lawrence<sup>86</sup>)

C PROLACTIN

1 Deficient lactation (Kurzrok, Bates, Riddle and Miller<sup>14</sup>)

D CORPUS LUTEUM HORMONE

1 After pains (Lubin and Clarke<sup>87</sup>) 2 Pernicious vomiting 3  
Premature labor

### CONCLUSION

The present status of gynecologic endocrine therapy places the physician in a dilemma. He cannot forswear these substances completely, because his patients will demand them. He cannot use them too frequently without appearing something of a charlatan to his more sceptical colleagues.

A year or so ago an editorial in the *Journal of the American Medical Association* (October 24, 1936) urged that only those physicians with facilities for critical study be encouraged to administer the new preparations and that other physicians should "cease their indiscriminate injections of unknown substances into unsuspecting patients." This advice cannot and should not be taken too literally. The physician with facilities for critical study has produced too many studies far from critical. Furthermore, a report of a percentage of successes with a new plan of therapy from a large clinic is only the beginning of its trial.

A new endocrine preparation, after one or two series of cases have been published, must be subjected to the test of its use in practice. Its final adoption will depend not upon whether a certain per cent of a series of fifty women are benefited, but whether it is sufficiently dependable to be used on a special case in whom an individual practitioner is individually interested. That the final test rests, therefore, with the general profession gives justification for the present cautious administration of these substances.

The use of the so-called sex hormones, however, involves certain

responsibilities. He who prescribes them must be certain of at least three things: (1) that conditions other than an endocrine disturbance have been excluded as the cause of the symptoms, (2) that experienced authorities regard the new material as safe, (3) that there is a rational basis and at least some expert testimony to the efficacy of the substance in treating the disease for which it is to be given.

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## THE PATHOLOGICAL RESPONSES TO VITAMIN DEFICIENCIES\*

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THE great reward of our efforts to understand the accessory food factors lies in improved nutrition. It is generally believed that we already see signs of this in an improved physical constitution of the younger generation, and a falling morbidity rate of diseases for which no specific control measures have been taken. Naturally this is of great interest to physicians. But there is another side to the subject which is of still greater interest, the morbid consequences of vitamin deficiency. While of distinctly less importance, this phase of the problem is so closely related to the problems with which physicians must constantly cope that it has attracted a great deal of attention.

Physicians have indeed become so actively interested in the vitamins that last year more than one thousand reports were published on the subject—ten times as many as were devoted to the virus diseases. The activity has become so intense that considerable confusion has necessarily followed. In such a situation it seems proper to consider representative vitamin deficiencies from the anatomical point of view, not only to demonstrate that thoroughly dependable anatomical criteria exist for several of these conditions, but also to show how the morphological evidence may be used further to advance our understanding of the subject.

A great deal has been known about the pathological anatomy of the deficiency diseases for a rather long time. The older pathologists had ample opportunity to study all of these diseases and to observe the lesions. Rickets was well understood long before vitamins were discovered and scurvy was not only accurately described but very keen inferences drawn concerning its nature and pathogenesis. Certain lesions were observed and largely forgotten. Thus, colitis cystica superficialis was rediscovered by Denton<sup>1</sup> as characteristic of acute pellagra many years after its original recognition.

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The earlier pathologists contended with two handicaps. In the first place, the deficiencies were usually multiple. This greatly complicated the lesions and led to marked difficulty in distinguishing between rickets and infantile scurvy. In the second place, most of their cases died of other, more dangerous complications, usually infectious diseases. Deficiency disease is relatively seldom the immediate cause of death, an observation which turns out to be of considerable importance to students of infectious diseases as well as nutritionists.

The great gift the biological chemists contributed was the opportunity for the study of controlled, graded cases of individual deficiencies and the exclusion of complicating diseases. Once this was achieved, the anatomical studies progressed rather rapidly, so that today it is possible to ascribe fundamental, specific effects on certain specialized tissues to each of several vitamins.

Vitamin A deficiency is an example. Some years ago the nutritionists spoke of this vitamin as a growth-promoting and anti-infectious food factor. This designation was based on the observation that when a young animal was deprived of vitamin A, growth ceased and the eyelids became matted together with exudate, while abscesses developed under the jaw. By the application of pathological criteria, it was discovered that the evidence of infection was only secondary to a remarkable metamorphosis or metaplasia of the epithelium of the ducts of the salivary glands and elsewhere. The normal columnar cells were observed to become replaced by stratified, squamous epithelium which rapidly became keratinized.

A keratinized cell is very durable and when found within the body is treated as a foreign substance. It is resistant to proteolytic enzymes and when such cells accumulate in a duct they obstruct the flow of secretions. Since an obstructed gland usually becomes an infected one, the anti-infectious nature of vitamin A was seen to be only an accidental, secondary effect of a much more significant morbid process. The eye lesions were due to a similar metaplasia of both the tear glands and the cornea. Other epithelial surfaces, including the urogenital tract and the respiratory passages, were found which behaved similarly. In man, the follicles of the skin become so filled with keratinized epithelium that they create the appearance of a toad's skin.

This is the essential lesion of vitamin A deficiency. It is a very sensitive criterion. A careful observer may establish its presence in the female

rat very early in deficiency by noting the prolongation of the stages of estrus characterized by keratinized vaginal cells. It is a yardstick by which we can determine a morbid consequence of vitamin A inadequacy in a given animal—but is it a *specific* effect?

Epithelial metaplasia was not a new lesion to pathologists. It had frequently been seen in various tissues. Its cause was, however, a complete mystery. Severe, generalized forms occurred in cases of prolonged, obstructive jaundice. In the days of intubation for croup it had at times been observed in the trachea where the cannula pressed against the mucosa, but efforts to produce it experimentally by cannulae only seldom succeeded. It was seen most often near foci of chronic inflammation and recently the endocrinologists had discovered that massive doses of theelin produced metaplasia in the endometrium of rodents.

We have tested the specificity of epithelial metaplasia in two ways. Whenever we discover a patch of metaplastic epithelium in tissues removed surgically, we search the patient for clinical evidence of vitamin A deficiency. This has not often been successful, possibly because of the delay between inauguration of hospital diet and our examination of the surgical specimen—a period long enough to allow of repair.

We have also tested experimentally the relative influence of vitamin deficiency, theelin and irritation.<sup>2</sup> The results of these trials have been most interesting. Irritation, as from a thread tied through the trachea, will produce metaplasia if the vitamin A intake is low, and will hasten the appearance of metaplasia if the deficiency be profound. But if the vitamin intake be large, neither mechanical irritation nor theelin dosing produces metaplasia. Indeed, an advanced stage of metaplasia produced by theelin will promptly undergo repair if ample vitamin be given. It therefore seems that vitamin A is the critical factor in experimental epithelial metaplasia.

However, these experiments go further. We have learned that more vitamin is needed to prevent metaplasia in rats given theelin than is required by normal animals and also that in the theelin-treated rats, the lesion of vitamin A deficiency occurs only in the uterus. In other words, theelin does not produce a systemic deficiency disease but only a local one, presumably by so exaggerating the rate of growth of the endometrial epithelium that the local requirements of vitamin are correspondingly exaggerated. The irritation experiments led to the same conclusion. Thus, the experiments seem to demonstrate a local morbid process, due

to a local deficiency in an animal receiving a maintenance dose of vitamin A. Such a conception extends the field of the pathology of the avitaminoses still further.

For example, it has been shown recently that many patients with renal calculus have stigmata of vitamin A deficiency (night blindness) and that most of these remain in this condition despite the prolonged administration of doses of vitamin A as great as 50,000 International Units daily.<sup>3</sup> It has been suggested that this is because they either do not absorb vitamin properly or fail to utilize it normally. It seems to me that we might consider that such persons have an *irreversible* form of vitamin A deficiency.

These new conceptions of the rôle of vitamin A, the local deficiency lesion and the irreversible one, might then be added to the list of deficiency effects due to faulty absorption, abnormal excretion by the kidneys, excessive destruction in the stomach or bowel, deficiency consequent to liver disease, the abnormally high requirement that alcoholics seem to have for vitamin B<sub>1</sub>, which is also present during pregnancy and infancy. It becomes evident that the known clinical forms of the deficiency diseases are the lesser part of our problem.

Vitamin C is likewise essential to the maintenance of a particular tissue—in this case the skeletal structures. The primary morphological effect of scurvy is seen in the bones, teeth, muscles and fibrous tissue. These are formed largely of intercellular materials which, in the absence of vitamin C, are of a different physical nature. They remain fluid, the form in which they are secreted. If vitamin be administered they rapidly solidify.

As far as may be judged by observation alone, this resembles the setting of a gel. It appears abruptly at some distance from the cell membrane, suggesting that the intercellular materials and not the cells are primarily affected. This theory is supported by the rôle the vitamin is known to play in oxidation-reduction phenomena in the tissues and the importance of hydrogen ion concentration to colloidal systems.

It is rather surprising how sensitive the anatomical criteria of scurvy are. A little practice and attention will disclose clues to this disease in much human material. Edwards Park's experience is instructive in this respect.<sup>4</sup> Two years ago, he and his colleagues analyzed 125 cases of scurvy. About one-sixth of these were found among 500 postmortem examinations which Dr. Martha Elliott, under the auspices of the United

States Children's Bureau, had started to collect at the New Haven Hospital. The work was later transferred to the Harriet Lane Home in Baltimore. The original purpose of the study was to determine the nature and extent of rickets by anatomic and radiographic examinations. Rickets was present in 27 per cent of this group, scurvy in 4 per cent. Of the nineteen cases having distinct anatomical evidence of scurvy, only two had been diagnosed before death and only seven by the pathologists who first studied the cases.

This is probably a rather representative record. It is worth noting two reasons which Park gives for the failures. In the first place, most of the children were suffering from another, more dramatic disease which absorbed the full attention of the physicians, and in the second place, the habit had been to look for scurvy among the children who were feeding problems, not, quite illogically as it turned out to be, among those having pneumonia and meningitis.

This interesting observation supports the recent demonstration that the vitamin C requirements of individuals sick from severe infectious diseases are abnormally high. Is there any morphological evidence to support this? There is the experience of Park, of course, and there is another possibility which might be considered with this in mind.

One of the lesions of scurvy is degeneration and fragmentation of the skeletal muscles. This was very conspicuous in years long past when severe scurvy was common. The muscles turned to "currant jelly" and were sometimes so extensively diseased that the patient became paralyzed. The lesion in these cases seems to be identical with what we have designated as Zenker's degeneration. It has a rather interesting history. Zenker was not the first to observe it but was the first to show its frequency, especially in typhoid fever. There it was so regularly present that it became an important postmortem clue to the disease.

Its most recent frequent occurrence was during the great influenza epidemic. Wolbach and Frothingham and MacCallum observed it in influenza deaths. Since, there have been but few and meager reports and while during the World War Beneke was able to find it in all infants dying of sepsis, it seems now to have become relatively uncommon or even rare.

The same lesion may be produced experimentally by vitamin C deficiency, by trauma, the injection of caustics and by a diet devised by Goettsch and Pappenheimer which is not deficient in the known vita-

mins But in man its occurrence seems to be largely limited to severe infectious diseases and to scurvy

The question seems unavoidable whether the infectious diseases with their high vitamin requirements and the older practice of feeding gruel and broth did not actually precipitate Zenker's degeneration by precipitating scurvy So far the evidence is circumstantial One is reminded of Coleman's demonstration twenty years ago of a negative nitrogen balance during typhoid fever, quite comparable to the negative vitamin balance found today Beneke's experience is wholly harmonious for the evident widespread occurrence of Zenker's degeneration in Germany during the War agrees with what we know of the incidence of mild scurvy during that time

Perhaps these several illustrations will amply indicate the engrossing fields of pathological study which the vitamins have opened to us and demonstrate how these factors may play a large part in conditions apparently quite removed from the deficiency diseases as we know them To me it seems to show likewise the necessity of a critical consideration of the diets used in most biological experiments, for the constitution of the diet modifies biological phenomena in many ways

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OUR VITAMIN B<sub>1</sub> SUPPLY IN RELATION  
TO HUMAN NEEDS\*

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THE vitamins must be viewed by the medical practitioner from a rather unique standpoint. They are not drugs and exhibit little pharmacological action in normal animals. They perhaps resemble hormones in respect to their high quantitative potency but differ from hormones sharply in that they are derived from external rather than internal sources. As components of foodstuffs, they have an apparent relationship to other components of food. One might plausibly think of some of them as related to the specific amino acids which have been found essential to proper nutrition. However, the vitamins differ from these components of food, according to the best existing evidence, in that they appear to be parts of necessary mechanisms rather than necessary building stones for the tissues.

Our topic this evening has to do with the choice and use of human food which is necessary to assure the maximum health and longevity. However, the mode of action of the vitamins is so fundamental to any sound philosophy in the matter that we must digress a moment to review the developments of the past two or three years concerning the physiological rôle of this category of substances. It has been shown that thiamin (vitamin B<sub>1</sub>) in the form of its pyrophosphate is a coenzyme, that is, a component part of enzyme systems having to do with carbohydrate metabolism. More particularly it has to do with the metabolism of pyruvic acid, a necessary intermediate in carbohydrate utilization. Carbohydrate metabolism is almost certainly a necessary function of nearly all living cells. The evidence is that thiamin pyrophosphate takes part in this metabolism of cells, whether they be those of bacteria, molds, fungi, higher plants, insects, or higher animals. The pathway whereby carbohydrate is metabolized appears to have much in common regardless of the type of cell with which one is concerned. Aside from the special function which each organ of a higher animal performs for the benefit

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of the body as a whole, there are processes of derivation of energy from carbohydrate which are carried on alike in each cell of all tissues. These are necessary for its own survival and vital activity. Thiamin, therefore, appears to be a fundamentally essential tool of metabolism, necessary for all living things.

What appears to be true for thiamin in high degree appears also to be true to a considerable degree for the other water soluble vitamins. Thiamin is merely the most conspicuous example, because nature's total supply is not much in excess of minimum needs and because the lack of no other accessory substance leads to so prompt, so profound and so universal a disaster.

It is consistent with this view that all plant and animal tissues contain this substance. However, the capacity for synthesis of the substance in nature is sufficiently limited so that no natural tissue is by accident super-rich in it. Whereas the majority of plant and animal tissues which are used as foods contain about one-half part per million of it, the richer foods contain only three to five parts per million. Notable among these are the seeds which constitute a principal repository of the substance in the plant world. The germs and bran coats of grains may contain thirty to fifty parts per million, these larger amounts being stored in the seed to care for the growth of the plant until it puts forth leaves to the sun and can then resume synthesis of the vitamin. Many of the lower plants have very meager capacity for its synthesis, some lack it entirely, none produce a plethora of it. The richness of brewers' yeast in vitamin content is primarily due to seizure of it from the grain wort in which the yeast is grown. If nature as a whole operates on an economy of scarcity with respect to this substance, it is not surprising that mankind should appear to do so also.

The foods may be divided into three groups

- A Thiamin-rich foods, notably seeds, lean pork, and to a lesser extent milk and the internal organs of mammals
- B Thiamin-poor foods, such as highly milled grains, hominy, macaroni, polished rice, white bread, sugar
- C Indifferent foods which comprise everything else except fats. These foods, such as fruits and vegetables, contain significant amounts of thiamin per unit of dry weight but do not provide a sufficient surplus to make up for the deficiencies of the thiamin-poor foods, unless the latter are used in relatively small quantities

D The Fats These do not require thiamin for their metabolism and in so far as they serve to displace foods of class B from the dietary, they have a very valuable protective effect

We recently have had occasion to reanalyze seventy diets associated with historical outbreaks of beriberi and about thirty diets associated with absence or recession of the disease. The diets in question are among those previously analyzed by Cowgill. After trying various indices, we found that the ratio between the thiamin content of the food and its non-fat calorie content is an excellent index of the appearance or non-appearance of beriberi. If the thiamin is stated in micrograms (millionths of a gram) and the calorific content in small calories, we get a relationship

$$\frac{\text{thiamin}}{\text{non-fat calories}} = 3$$
 as representing the borderline between beriberi and non-beriberi

This index also fits quite well the diets of the working classes in the United States, to judge from a considerable number of them to which it has been experimentally applied. The contrast between the Oriental beriberi-producing diets and poor class American diets is not great with respect to thiamin content. The latter diets owe such superiority as they possess as much to the presence of larger amounts of fat as they do to the presence of larger amounts of thiamin. American diets in which white bread, corn meal and like products make up a large part of the calories are near the beriberi borderline. The diets of more prosperous people show a considerably larger margin of safety due principally to the lesser proportions of starchy foods. It should be said, however, that many of the Oriental diets used by peoples who are not addicted to the milling of grain often contain as much or more thiamin than the average American diet.

An attempt has been made by Cowgill to relate the thiamin requirement to the individual weight. He concluded on the basis of animal experiments that the thiamin requirement of an individual is proportional to weight<sup>5/3</sup>, that is, that in a series of individuals the requirement rises much more rapidly than the weight. The experiments in question were performed before it was well recognized that there is a large number of B vitamins. In the light of recent knowledge, the basal diets which were used were deficient with respect to several of these factors. We believe that the apparent rising proportional require-

ment with rising weight is due to the fact that larger doses of crude vitamin were necessary, not to supply sufficient thiamin, but to supply sufficient, or more nearly sufficient, amounts of the other B factors which were also present in the crude product, but in lesser proportions

Cowgill recognized that the requirement per unit of body weight is much larger for small species of animals than for large species, an idea which has general support. Combining these two theses, he gives us a picture of animal needs *rising* with individual weight within a species but *falling* as individual weight rises from species to species. This does not seem reasonable for it implies that species divisions represent sharp breaks in respect to metabolic economy in the animal world, whereas we have long been accustomed to think of the various species as physiologically akin, differing from one another by small gradations.

If one abandons the idea of the vitamin requirement rising in proportion to weight<sup>5/3</sup>, as one is justified in doing on the basis of recently gained knowledge with regard to the multiplicity of B vitamins, one arrives at a much more reasonable and consistent picture. It is, that the required proportion of thiamin to non-fat calories of the food is substantially constant for all species and all weights. The quantity of food which is required, and therefore the *quantity of thiamin* per unit of body weight, rises in a general way as the weight falls whether within a species or from species to species, approximately in proportion to weight<sup>2/3</sup>. This is a reflection of the fact that the body surface and the consequent heat loss from the surface rises as size decreases. The increase of food requirement (calories) with diminishing size is, of course, not a precise proportionality as it is affected by many factors, such as activity, habitat, or fur covering. In a rough way, however, it is true for warm blooded animals.

As far as the *proportion of thiamin* in the food is concerned, the requirement of all warm blooded animals is substantially the same, as far as our present knowledge permits us to judge. (An adjustment for proportion of fat in the customary food would be necessary.) One is tempted to surmise that the animal world gets as much thiamin as the plant world is able to supply and that this amount affords little margin above the requirements for health and well-being of all the creatures which evolution has produced. In favor of such a view is the fact that enrichments of supposedly normal diets have often been observed to result in superior performance. Some plants which can synthesize thiamin

also respond favorably to a supplemental external supply

Animals are not economical of thiamin but tend to waste any excess above their needs. An increase in the intake is promptly reflected in an increase in the excretion in the urine. Storage in the body against a later time of need is quite limited. In quantitative terms, the human requirement for the prevention of beriberi is about one milligram for each 3700 non-fat calories of food intake. For diets containing large proportions of starch and small proportions of fat, such as prevail for a great part of the working population of the world, the minimum daily requirement per adult is apparently not far from 0.6 milligrams or roughly 200 International Units per day for a 2500 calorie intake.

We have previously emphasized the bran coats and germs of seeds as the principal repository of thiamin in foodstuffs of plant origin. As Robbins and others have shown, excised tomato roots are able to grow in artificial nutrient media in proportion to the thiamin added, over a wide range of values. It seems clear that thiamin is present in the seed to enable the plant to metabolize the starch placed there for its nourishment during its early weeks of growth. If plants, which can synthesize thiamin, are compelled at certain stages to fall back upon reserve stores of thiamin in order to utilize starch, it seems utter folly for mankind to consume the starch and carefully to discard the mechanism provided by nature for its metabolism.

The foregoing view of nature's economy of thiamin (and to some extent all other water soluble vitamins) rationalizes vitamin therapy much more satisfactorily than has heretofore been possible. It is no longer mere superstition that an abundant supply of thiamin may have therapeutic value in conditions which are not necessarily associated with any *sub-average* intake of thiamin in the food supply of the patients. The intake may be merely *sub-optimal*. If thiamin constitutes a necessary mechanism of metabolism for all cells, it is readily conceivable that an increase in the supply of this essential substance may result in an improved functional performance of whatever organ may be operating at low efficiency. Thiamin is not peculiarly a nerve vitamin, nerve tissue is merely peculiarly susceptible to the effects of a metabolic disturbance which simultaneously affects adversely but less conspicuously the functioning of all other organs.

In closing I want to extend my sympathy to the medical practitioner who must endeavor to keep track of a host of new therapeutic agents,

many of which bear purely arbitrary names, such as vitamin A, B, C. To add to his troubles, their potencies are often expressed in arbitrary units which are related, not to the performance of human beings, but to the daily needs of some small experimental animal. In addition, two or three different sets of units are often used. It may be a memory aid for such practitioners to remark that, whatever system of units is used for the vitamins, it requires several hundred units of any of the vitamins to afford a significant dose for a human adult. In the case of vitamin A, several thousand units are needed.

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### DEATHS OF FELLOWS

CORILLOS, POL N, 894 Madison Avenue, New York City, born in Patras, Greece, November 2, 1879, died in New York City, July 26, 1938, graduated in medicine from the University of Athens in 1901 elected a Fellow of the Academy March 7, 1929

Dr Corillos was a member of the State and County Medical Societies, a Fellow of the American Medical Association and the American College of Surgeons, a member of the American Society of Thoracic Surgeons and the New York Society of Thoracic Surgeons. He was Director of Thoracic Surgery at the Metropolitan, Sea View and U S Veteran's (Castle Point) Hospitals, Associate Surgeon and Director of Thoracic Surgery at Polyclinic Hospital, Consulting Thoracic Surgeon to Broad Street and Staten Island Hospitals, Consulting Surgeon to St Luke's Hospital at Newburgh, and Thoracic Surgeon to the Out-Patient Department of the New York Hospital

FRANKLIN, MELVIN M 1911 Spruce Street Philadelphia, Pennsylvania, born in Philadelphia, Pennsylvania, August 13, 1874, died in Point Pleasant, New Jersey, July 31, 1938, graduated in medicine from the University of Pennsylvania in 1895, elected a Fellow of the Academy January 6, 1910

Dr Franklin was visiting orthopedic surgeon to the St Joseph's Hospital and consulting surgeon to the St Joseph's, Mercy and Jewish Hospitals of Philadelphia and the Bamberger Memorial Hospital of Atlantic City, New Jersey

He was a Fellow of the American Medical Association and the American College of

Surgeons and a member of the County and State Medical Societies

MOONEY, HENRY WALTON 1 West 85 Street, New York City, born in New York City, July 19, 1861, died in New York City, July 17 1938 graduated in medicine from the University of New York in 1891, elected a Fellow of the Academy October 6, 1904

Dr Mooney was a member of the State and County Medical Societies

STEWART, JOHN DILLON 550 Park Avenue, New York City, born in Newark, Ohio, November 22, 1880, died in New York City, August 3, 1938, graduated in medicine from the Medical College of Indiana in 1905, elected a Fellow of the Academy February 7, 1938

Dr Stewart was attending surgeon to the Post-Graduate Hospital and professor of clinical surgery at the Graduate School, Columbia University, College of Physicians and Surgeons

He was a Fellow of the American College of Surgeons and the American Medical Association, and a member of the American Proctologic Society and the County and State Medical Societies

WIENER, JOSEPH 30 East 40 Street New York City, born in New York City, March 24, 1872, died in Lawrence, Long Island New York August 28, 1938 received the degree of Bachelor of Arts from the College of the City of New York in 1890 and graduated in medicine from the College of Physicians and Surgeons, Columbia University, in 1893 elected a Fellow of the Academy February 1, 1900

Dr Wiener was associate attending surgeon to the Mount Sinai Hospital for many years. He was a Fellow of the American College of Surgeons, a Fellow of the American Medical Association and a member of the New York Surgical Society and the County and State Medical Societies

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THE CHEMISTRY AND BIOLOGY OF MALE  
SEX HORMONES\*

F C KOCH

Professor of Biochemistry The University of Chicago

INTRODUCTION

WHAT is now interpreted as the general physiological response to a lack of male sex hormone in the male is no doubt the earliest observation in endocrinology in man and in domestic animals. Castration was practised among the ancients, probably earliest in China. In the Bible we find reference to eunuchs "so born from their mother's womb," eunuchs made by man, and "eunuchs which made themselves eunuchs for the Kingdom of Heaven's sake." While the motives for castration in men were in the main to prevent reproduction, the profound general physiological changes must have been observed in man and were intentionally produced in domestic animals. It is not surprising that these rather accidental observations early led to attempts to replace the missing organs by homo-transplantation. The first testis transplantation on record appears to be by John Hunter in hens in 1762,<sup>1</sup> but the first true replacement studies by transplantation were conducted by the German physician, Berthold in 1849, in the capon.<sup>2</sup> He concluded that the regeneration of

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\* Lecture delivered April 21, 1938



Fig 1

the capon's comb by the testis transplant must be due to "the influence of it upon the blood, and then to the influence of the blood on the organism as a whole, with the nervous system no doubt playing a very important rôle" In spite of these early physiological studies on the testis many less obvious endocrine organs have yielded their secrets to our combined biological and chemical attack much more readily than the testis The reasons for slow progress in the case of the testicle are now clear because we know that testis tissue, contrary to most other endocrine organs and contrary to most earlier claims, contains its hormone in such low concentrations that considerable fractionation and concentration must be accomplished before it can be detected by biological or chemical methods

#### THE ISOLATION OF PURE ANDROGENS AND THEIR STRUCTURAL FORMULAE

The first investigator to contribute materially to this phase of the problem was McGee<sup>3,4</sup> who also first introduced the use of the brown leghorn capon for assay purposes Following his discovery, detailed quantitative studies on the comb-growth reaction in the capon led to the development of several very satisfactory quantitative assay methods for androgens These methods have been used to great advantage in studying



Fig 2

the distribution of androgens, in the fractionation of extracts, and in the separation of pure androgens. A qualitative result from the intensive treatment over a period of eighteen days is shown in Figs 1 and 2 and the quantitative relation between dosage and comb-growth response by the curve in Fig 3.<sup>5</sup> With these methods developed it was soon found that men's urine is a good source for androgenic activity and it was also found that testis-tissue concentrates which had been standardized by the capon method could be used to regenerate the atrophied accessory sex organs of castrated rats and guinea pigs.

From this time on rapid strides were made in the chemistry of androgens. Butenandt<sup>6</sup> was the first to separate androsterone (III, page 659) in pure crystalline form from human urine-concentrates. In 1934 he and Tscherning<sup>7</sup> assigned the correct formula thereto (III) and also showed its relation to dehydroandrosterone (II), another androgen from human urine. The suggested relation of these compounds to cholesterol (I) is obvious, but the proof of this relationship involved a number of possible isomerisms, a problem which was beautifully solved by the classical work of Ruzicka and his associates.<sup>8</sup> These investigators assumed that if androsterone (III) could be formed from cholesterol (I), it

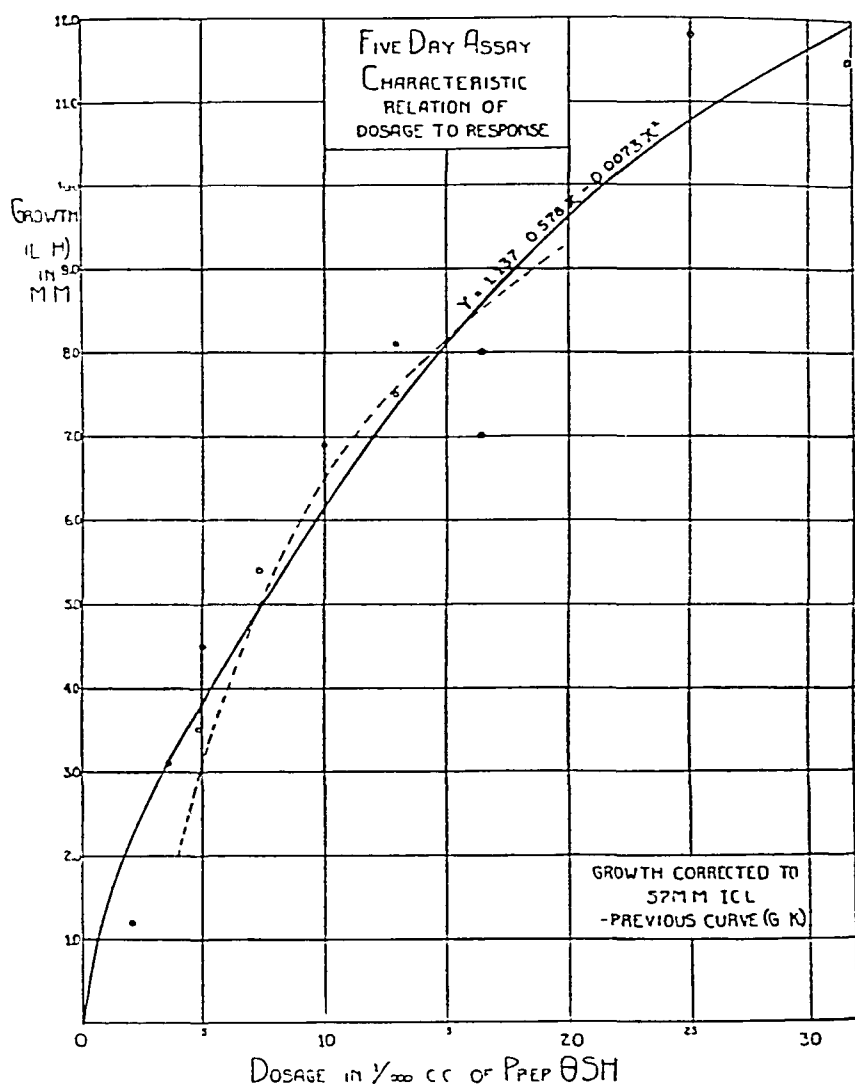
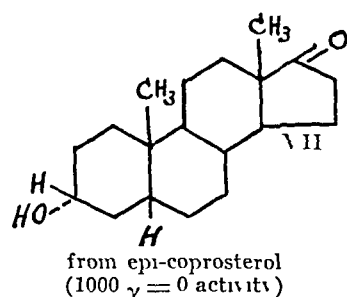
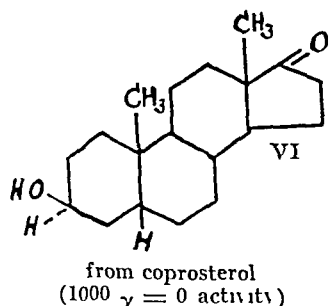
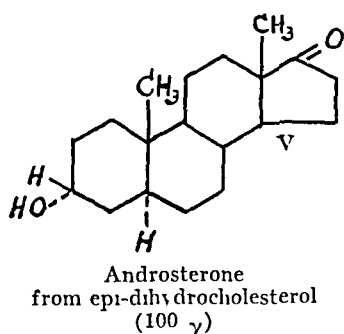
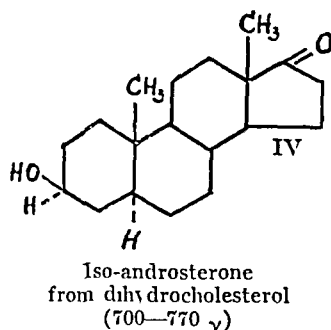
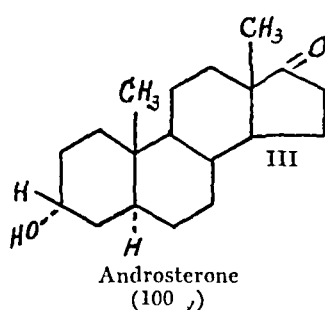
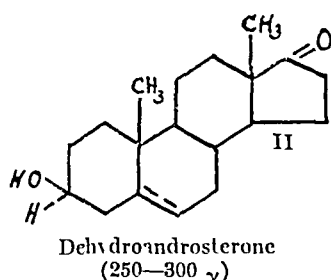
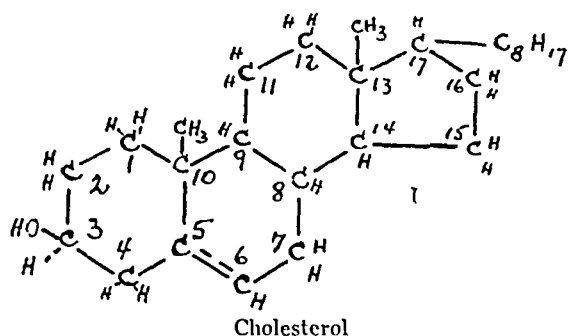


Fig 3

might have the structure of one of the four possible isomers (IV, V, VI, and VII) The four isomers were prepared and V was found to be identical chemically and in biological activity with the Butenandt product obtained from urine The important steps in the synthetic degradation of cholesterol to androsterone are given on page 661

When androsterone was first separated, it appears to have been quite generally assumed that male-hormone activity probably would be limited to it and to dehydroandrosterone In other words, it was thought that

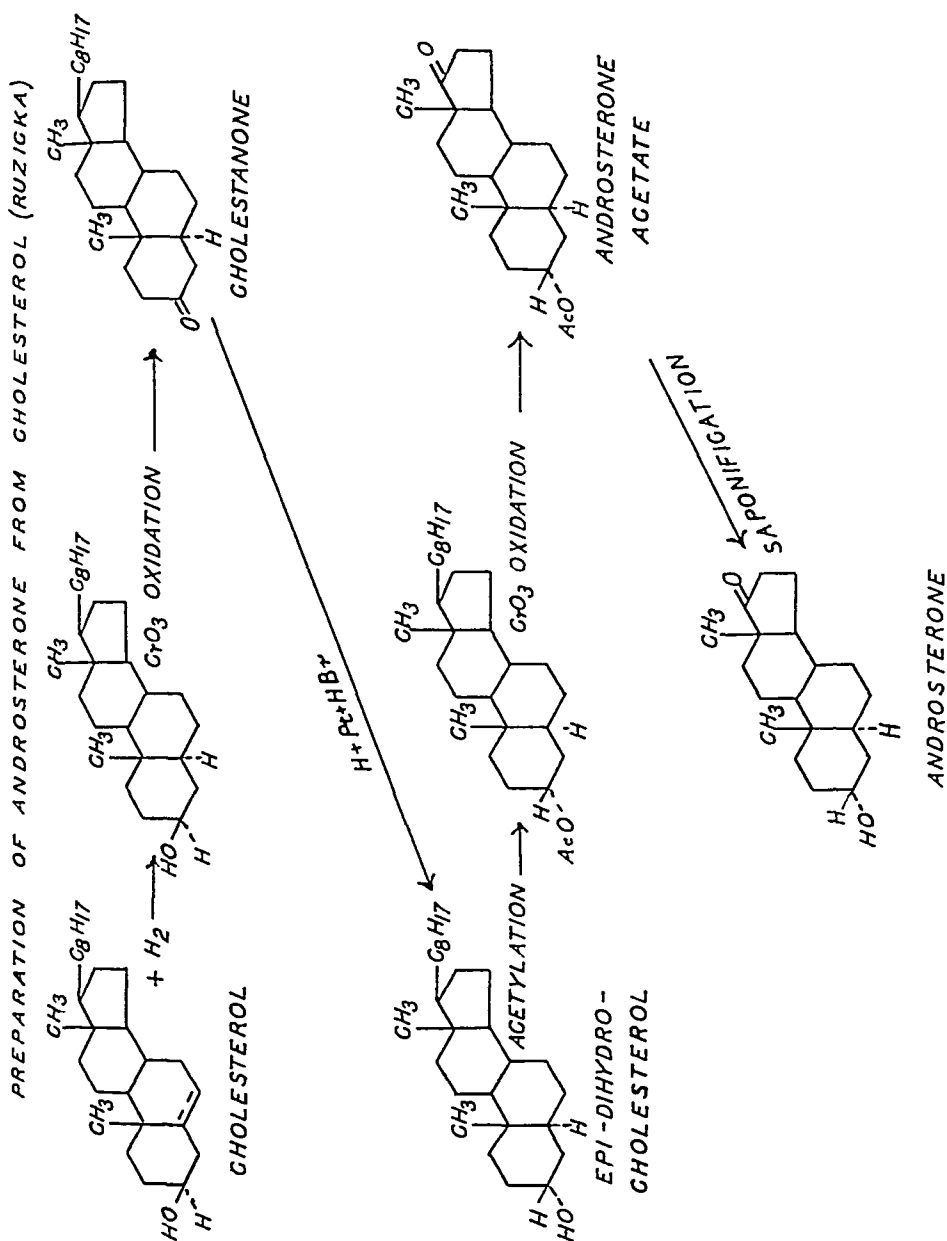
STRUCTURAL RELATIONS BETWEEN CHOLESTEROL AND ANDROGENS



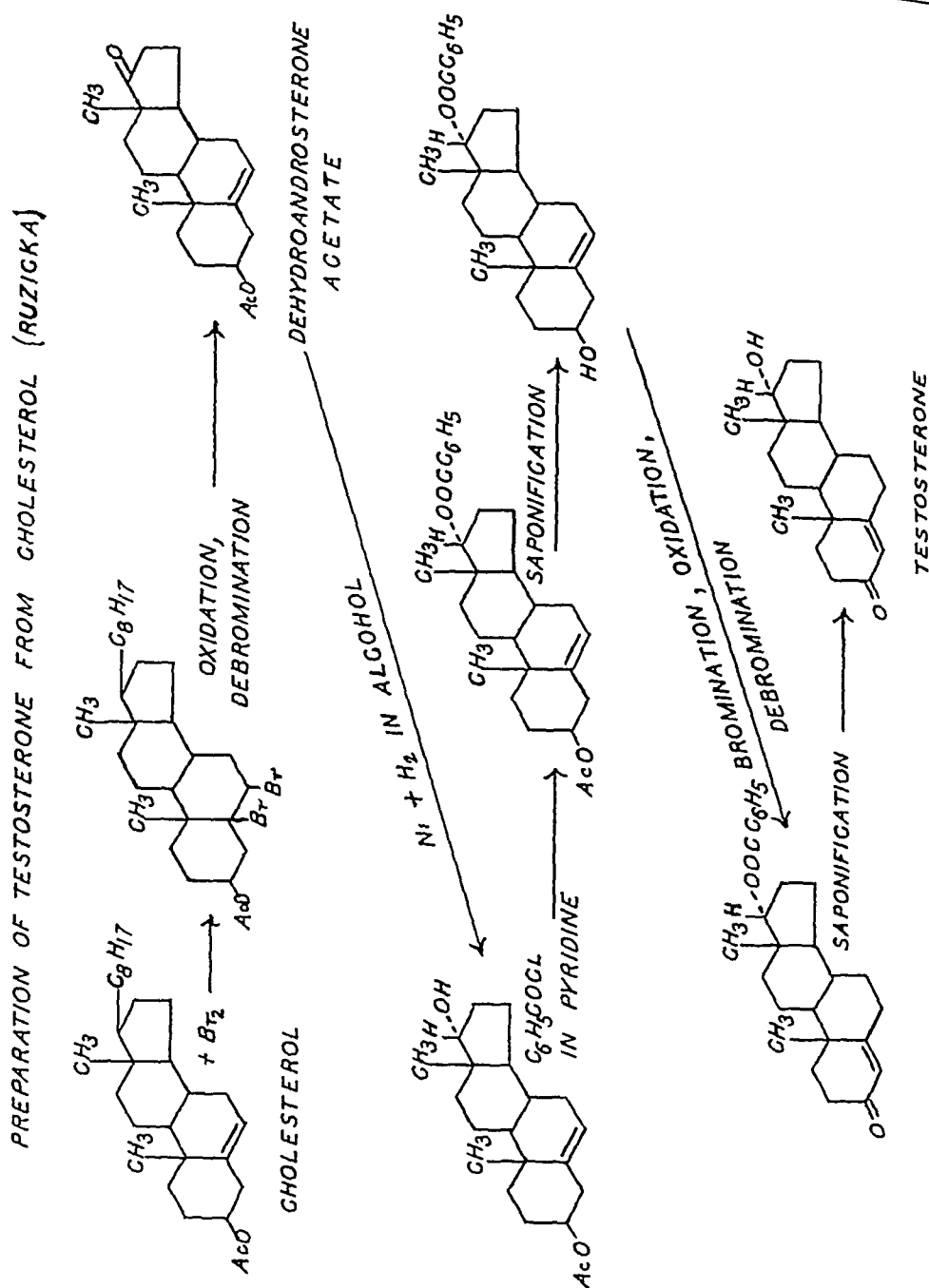
The  $\gamma$  values represent the equivalent of the international capon unit or 100  $\gamma$  of androsterone

it probably represented the true secretion from the testicles. However, Gallagher and I<sup>9</sup> had already obtained concentrates from bull testis-tissue which were five to ten times as potent per unit weight as crystalline androsterone and we had also demonstrated a difference in the action of alcoholic potassium hydroxide on testis-tissue and urinary concentrates of androgens.<sup>10</sup> The former was destroyed, but the latter was not. Furthermore, Laqueur and his group<sup>11</sup> had shown by comparative assays on capons and castrated rats that the ratio expressed as rat units over capon units for various fractions and concentrates showed tremendous fluctuations. Stimulated by these findings, David, *et al*<sup>12</sup> finally succeeded in separating the third androgen, testosterone, from bull testis-tissue. He did not determine its structure but within a very short time after he had announced his discovery, the Butenandt<sup>13</sup> and Ruzicka<sup>14</sup> groups independently reported the preparation of the identical substance by the synthetic degradation of cholesterol. The fact that the androgenic activity in testis-tissue concentrates had been found to be alkali-labile stimulated the organic chemist to attempt to produce from cholesterol a variety of derivatives which one would expect to be alkali-labile. The probable structure of such a group was indicated by the observation that progesterone (XVIII, p 666) was known to be alkali-labile. Hence the attempts to prepare  $\Delta^4$ -androstenone-3 derivatives of various kinds. Of these,  $\Delta^4$ -androstenolone-17,3 proved to be identical with testosterone (VIII). The steps involved in the synthetic degradation of cholesterol to testosterone are given on page 662.

With the advancement of our knowledge of the chemistry of sterols and bile acids, which was gained mainly through the interest aroused in these substances as a result of vitamin D and sex hormone studies, the organic chemists soon produced innumerable compounds more or less related to the natural androgens. Naturally the isolation of other androgens from natural sources also became less difficult. To date over fifty such androgenic substances are known. On pages 663 and 664 a few of the more typical androgens are given, they are grouped as saturated and unsaturated compounds. The potencies are expressed in micrograms equivalent to the international unit of 100 micrograms of androsterone as assayed on the capon and in most cases also the activity as determined in the rat. A study of these pages shows that stereoisomerism is a very important factor in determining the activity of these compounds and that the relative potencies of these substances on capons and rats vary



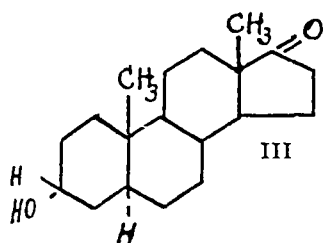
considerably. Thus, in the saturated series, the active forms are those compounds which have the hydrogen on carbon 5 in a *trans* position with reference to the CH<sub>3</sub> group on carbon 10. Expressed in other words this means that the saturated compounds which have been derived from dihydrocholesterol or epidihydrocholesterol are likely to be more active



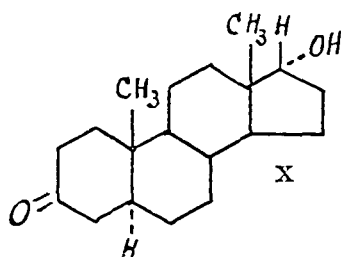
than the isomers obtained from coprosterol or epicoprosterol. This is an excellent illustration of the delicate and detailed architecture of some of our physiological mechanisms.

The configuration of the secondary alcohol groups in positions 3 and

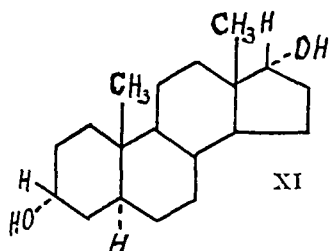
SOME SATURATED ANDROGENS



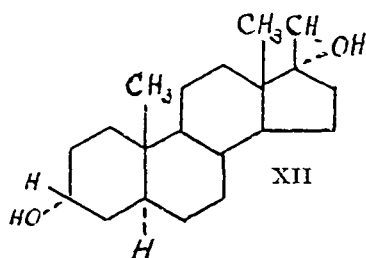
Androsterone  
(from men's urine)  
(100  $\gamma$ )\*  
(500  $\gamma$ /10/68 mg)†



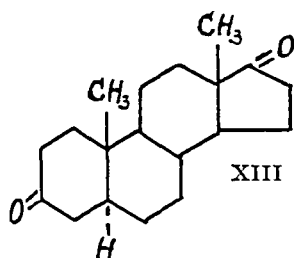
Androstanolone-17 trans, 3  
(not found in nature)  
(25–30  $\gamma$ )  
(rat test<sup>2</sup>)



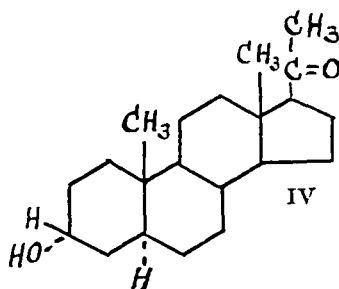
Androstenediol-3 cis, 17 trans  
(not found in nature)  
(20–35  $\gamma$ )  
(100  $\gamma$ /10/43 mg)



17-Methyl (cis)-Androstenediol-  
3 cis, 17  
(not found in nature)  
(25–40  $\gamma$ )  
(200  $\gamma$ /10/35 mg)



Androstenedione-3,17  
(not found in nature)  
(120–125  $\gamma$ )  
(200  $\gamma$ /10/29 mg)

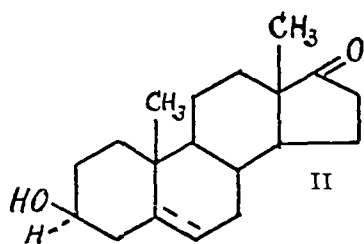


Epi-allo-pregnanolone-3,20  
(from women's pregnancy  
urine)  
(androgenic in capons and  
rats)

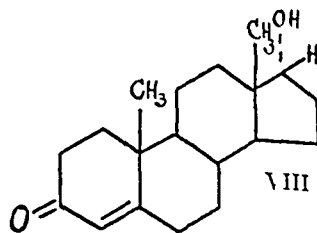
\* equivalent of international unit on capon

† per day for 10 days in rat with weight of seminal vesicle in milligrams

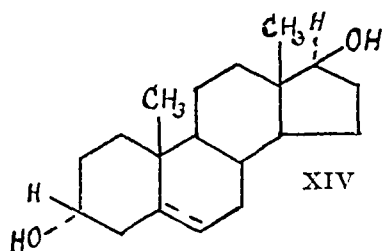
## SOME UNSATURATED ANDROGENS



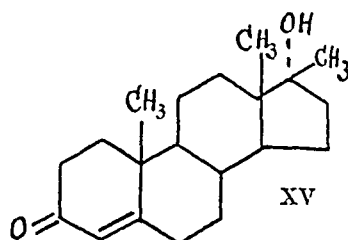
Dehydroandrosterone  
(from men's urine)  
(250—300  $\gamma$ )\*  
(500  $\gamma$ /10/16 mg)†



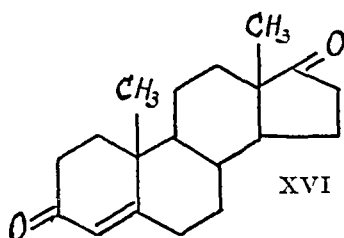
Testosterone  
(from bull testis-tissue)  
(13—16  $\gamma$ )  
(50  $\gamma$ /10/150 mg)



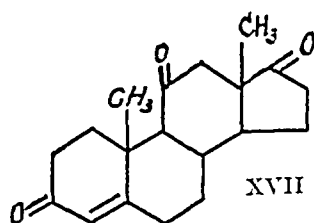
$\Delta^5$ -Androstenediol-3 trans, 17 cis  
(not found in nature)  
(235—650  $\gamma$ )  
(2000  $\gamma$  no action in rat)



17-Methyl (cis), Testosterone  
(not found in nature)  
(10—15  $\gamma$ )  
(rat test?)



$\Delta^4$ -Androstenedione-3,17  
(not found in nature)  
(100—120  $\gamma$ )  
(100  $\gamma$ /10/50 mg)



Adrenosterone  
(from suprarenal cortex  
and from cortical hormone  
by oxidation)  
(500—600  $\gamma$ )  
(rat test?)

\* equivalent of international unit on capon

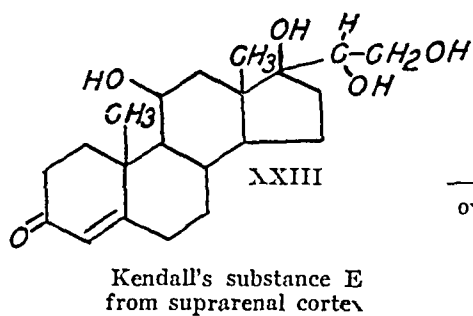
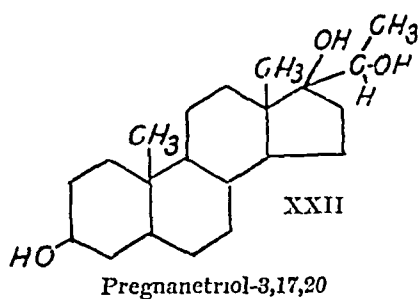
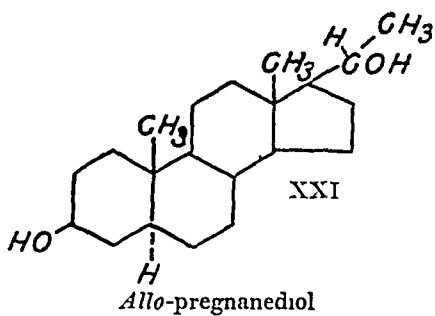
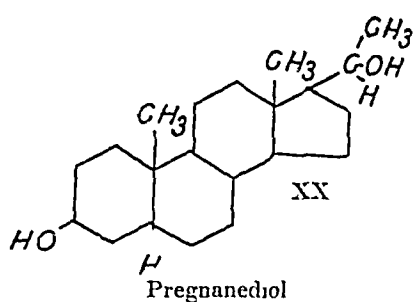
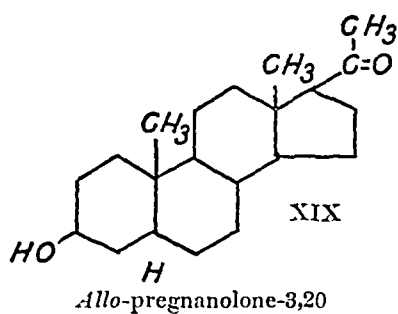
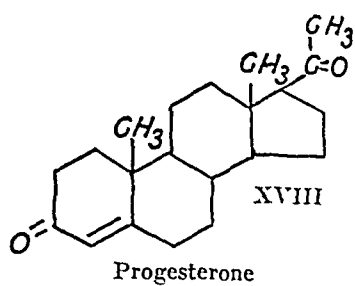
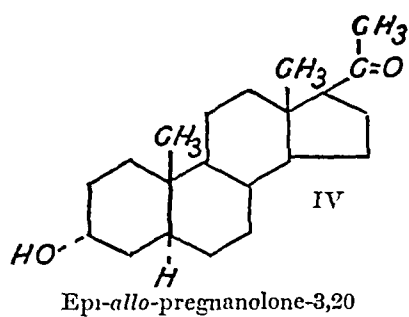
† per day for 10 days in rat with weight of seminal vesicle in milligrams

17 are equally important in determining the potency. Please note that in the saturated and also in the unsaturated series the more active compounds have the OH groups in the *trans* position (indicated by -- bond) with reference to the nearer CH<sub>3</sub> group. Compare II and XIV with III and XI. A very striking example is testosterone which has been obtained in the *trans* and *cis* forms by Ruzicka and Kagi.<sup>15</sup> These authors report that the *trans* or natural form of testosterone is approximately thirty times as potent as the *cis* form also obtained by synthetic methods.

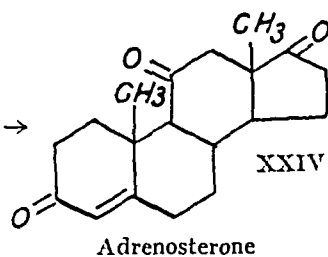
Of particular biological interest are epi-*allo*-pregnanolone-3,20 (IV) and adrenosterone (XVII). The former was first isolated from human pregnancy urine and thus accounts in part for the androgenic material found in pregnancy urine. It is interesting to note that an isomer thereof, *allo*-pregnanolone-3,20 (XIX) has been obtained from corpus luteum extracts, that two closely related compounds, pregnanediol-3,20 (XX) and *allo*-pregnanediol-3,20 (XXI) have also been found in pregnancy urine and that a third compound (XXII) has been separated from the urine of a woman afflicted with an adrenogenital syndrome.<sup>16</sup> The structural relations between these compounds shown on page 666 indicate that it is fairly safe to state that these substances probably represent waste products from progesterone secreted by corpus luteum tissue.

Adrenosterone (XVII) and pregnanetriol-3,17,20 (XXII) are of particular interest because their presence in the urine may reflect in part the cause for the hirsutism in certain cases of adrenal tumors and it also suggests that the adrenals may be responsible for part of the androgenic activity found in normal urines from men and women and especially from human castrates. The probable chemical relations between the adrenal cortical precursor, Kendall's compound E, and adrenosterone, are indicated by XXIII and XXIV. It is also obvious that XXII may possibly also be formed from compound XXIII and hence from suprarenal cortical tissue rather than from corpus luteum tissue.

This discussion leads us to the conclusion that at present six androgens have been found in nature and that four of them have been isolated from human urine. Only androsterone and dehydroandrosterone have been separated from men's normal urine. Whether all the androgenic activity from normal men's urine resides in these compounds or whether others contribute, remains to be determined. Although normal women also excrete large amounts of androgenic material, the exact nature thereof has not been determined. Thus far, no pure androgen has been



oxidation →



separated from the urine of a normal non-pregnant woman. However, in the pregnant woman, Marker, Kamm, *et al*<sup>17</sup> separated epi-allo-pregnanolone-3, 20 from the urine as one of the androgens. In pathological urines we undoubtedly have varying amounts of adrenosterone and pregnanetriol-3, 17, 20 in addition to androsterone, dehydroandrosterone, and many other possible compounds of androgenic character.

That the normal type of androgen may be increased in concentration in pathological conditions is well illustrated by Callow<sup>18</sup> who separated 110 milligrams of dehydroandrosterone in pure form from one liter of urine from a six year old girl afflicted with an adrenal tumor. This represented 70 per cent of the total androgenic material. In other words, this child excreted approximately 600 international androgenic units per liter of urine, whereas the normal child of that age might possibly excrete 2 to 10 units. In view of the possibilities of complex mixtures existing in various urines in various proportions it is very probable that future advances in the quantitative studies on urine will depend to a large extent on our ability to differentiate quantitatively between the different androgens. However, for the present we must be content with the estimation of the total androgenic activity in tissue, body fluids, and excretions in our attempts to correlate the quantitative information with various endocrine disturbances possibly involving the gonads. Our first consideration is the type of test animal to be used to give most reliable comparative analyses and the second the completeness of extraction of the tissues or fluids.

*Complications involved in the rat seminal vesicle or prostate reaction to androgens.* First it is necessary to present briefly the limitations of the rat assay method for comparative studies on crude concentrates from various sources. It may be recalled that in the early studies on concentrates Laqueur and his associates observed striking irregularities in comparing the results obtained by the rat method with those found by the capon comb-growth reaction. After the pure androgens were made available it became obvious that these irregularities are introduced mainly by the rat test. This was first clearly demonstrated by the Laqueur group<sup>19</sup> who discovered that a non-androgenic fatty-acid fraction ("X factor") from bull testis-tissue when injected with a given amount of testosterone increased the seminal vesicle weight response in the rat three to four fold over the effect of testosterone alone. The exact nature of the Laqueur "X factor" does not appear to have been determined, but

TABLE I

*The influence of the daily injection of alcohols, fatty acids or esters on the response of the castrated rat to 10 daily injections of 50 Y testosterone*

ALCOHOL ACID OR ESTER	DAILY AMOUNT	NUMBER OF RATS	SEMINAL VESICLES	PROSTATE
	mg		mg	mg
Sesame oil alone	0	3	14	41
Testosterone alone	0	4	42	66
Ethyl alcohol, $C_2H_5OH$	50	2	82	98
Propyl alcohol, $C_3H_7OH$	50	2	117	156
Propionic acid, $C_3H_7O_2$	50	3	117	158
Hexyl alcohol, $C_6H_{13}OH$	50	4	95	125
n-Hexanoic acid, $C_6H_{11}O_2$	50	4	95	140
Cetyl alcohol, $C_{16}H_{33}OH$	50	4	125	165
Palmitic acid, $C_{16}H_{31}O_2$	50	4	235	210
$\omega$ -Hydroxy palmitic acid, $C_{16}H_{31}O_3$	25	2	150	158
Stearyl alcohol, $C_{18}H_{37}OH$	50	4	200	220
$\gamma$ -Hydroxy stearic acid, $C_{18}H_{35}O_3$	50	4	210	220
Ethyl propionate	50	2	33	66
Methyl stearate	50	2	43	89
Monostearin	50	4	40	76

Compiled from Miescher, Wettstein, and Tschopp, *Biochem J*, 1936, 30 1970 )

a number of pure substances can be substituted for the "X factor" and produce the same enhancing effect in the rat. Among these substances are aliphatic fatty acids, primary alcohols, hydroxy fatty acids, and estrogens. At least two substances have been found to decrease the seminal vesicle weight response. These substances are glycerol and paraffin oil. The decreased response with these vehicles for androgens might be attributed to too rapid absorption from glycerol and too slow absorption from paraffin oil to produce the optimum physiological response. This explanation does not seem completely satisfactory, however, because the addition of the proper fatty acids to these solutions increases the action of the testosterone three to four fold on the seminal vesicles. The data given in Tables I and II illustrate these statements. The mode of action of the fatty acids and primary alcohols is also by no means clear because only certain androgens are activated by these compounds. Among those not activated by the "X factor" or fatty acids are androsterone, urinary concentrates, androstanedione, 17-*cis*-testosterone, and testosterone acetate.

Esterification of testosterone also increases the potency of the prod-

TABLE II

The influence of the daily injection of various solvents on the response of the castrated rat to 10 daily injections of testosterone or testosterone acetate

	DAILY DOSE OF TESTOSTERONE OR TESTOSTERONE ACETATE	NUMBER OF RATS	SEMINAL VESICLES	PROSTATE
	γ		mg	mg
Sesame oil	0	3	14	41
Testosterone in sesame oil	50	4	42	66
Testosterone in 50 p c glycerol	50	2	16	46
Same + 50 mg ricinoleic acid	500	2	20	—
	50	2	221	205
Testosterone in paraffin oil	50	2	15	44
Same + 50 mg palmitic acid	50	2	126	145
Testosterone acetate in sesame oil	50	8	218	241
	200	2	383	357
Same + 50 mg palmitic acid	50	2	210	279
	200	2	302	334
Testosterone acetate in 50 p c glycerol	50	2	12	36
	125	2	45	72
Same + 50 mg ricinoleic acid	125	2	215	283
Testosterone acetate in paraffin oil	50	2	65	105
	200	2	252	293

(Compiled from Miescher, Wettstein, and Eschopp, *Biochem J*, 1936, 30 1977)

uct A given weight of testosterone propionate when injected into the young castrated rat produces three to four times the weight of seminal vesicle as is produced by the same weight of free testosterone This enhancing effect of fatty acids, alcohols, and esterification is not manifest in the capon comb-growth method In the capon method a slight delay in reaching the maximum comb-growth for a given dose may be observed with testosterone esters but this is not serious for the lower molecular weight fatty acids For the higher molecular weight esters the response is very much delayed and of lower order That is what one would expect because the dose of actual testosterone in a given weight of ester is diminished as the molecular weight of the fatty acid is increased Table III and Fig 4 give the experimental data for these conclusions

The capon not only responds more quantitatively per molecule of androgen whether free or esterified, but also quantitatively the same to

TABLE III

*Comparative assays of testosterone esters on capons*

SUBSTANCE	DAILY AMOUNT EQUIVALENT TO ONE INTERNATIONAL ANDROGENIC UNIT OR $\approx 170\mu$ ANDROSTERONE	TIME OF MAXIMUM EFFECT
	$\gamma$	days
Testosterone	15	6
Testosterone formate	20	7
Testosterone acetate	20	7
Testosterone propionate	20	9
Testosterone butyrate	60	12
Testosterone isobutyrate	70	13
Testosterone valerate	200	14
Testosterone isovalerate	250	15
Testosterone n-decanoate	350	16
Testosterone palmitate	>1000	—
Testosterone stearate	>1000	—
Testosterone benzoate	>1000	—

(Compiled from Miescher, Wettstein, and Ischopp, *Biochem J*, 1936  
80 1977)

a uniform weight of testosterone whether with or without fatty acids or the "X factor"

From these experiences and many other observations it may then be concluded that at the present time the capon comb-growth response is a more satisfactory method for the quantitative assay of total androgenic activity in crude concentrates which are likely to contain various androgens as well as many other substances which may enhance or retard the response in the rat

*Quantitative studies on the distribution of androgens* We are now in a position to discuss the completeness of extraction of androgens and the possibility of androgens occurring in conjugated compounds in tissues and biological fluids

*Testis-tissue* Although the early reports, which were based on poor biological observations, led us to expect a relatively high concentration of hormone in testis-tissue, repeated attempts to increase the yield of androgen from bull testis-tissue by more extensive extraction or by hydrolysis of the aqueous phase before extraction by alcohol or benzene detect neither increases in androgen nor hydrolyzable conjugated forms thereof. The yield is practically the same as usually found by the routine McGee procedure and varies from three to nine international androgenic

units per pound of bull testis-tissue. If this is expressed in milligrams it calculates from 90 to 270 milligrams of testosterone per ton of tissue. It is of course still possible that a conjugation of an androgen with protein may exist and that we have not been able to break the hypothetical linking and still retain the activity. It is also of special interest that testis-tissue from calves and fetal calves actually yield higher amounts of androgens by the routine procedure. Why male hormone should be present in fetal testis-tissue in higher concentrations than in the mature animal is

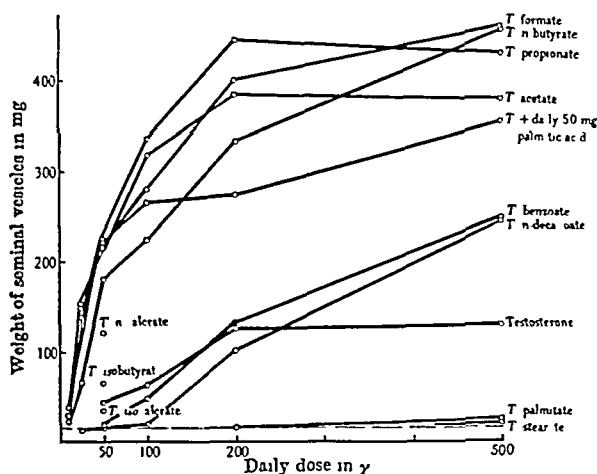


Fig. 4

rather perplexing. It seems to me that we must resort to the assumption that it is elaborated or stored in the organ but apparently not secreted in adequate amounts to influence the accessory sex organs.

**Blood.** The early claims for the high concentration of male hormone in blood also have not been confirmed. Recent studies by my associates\* and myself also fail to detect a conjugated form of androgen in human blood. We had considerable difficulty in working up enough blood to warrant accepting the growth response as significant. We found it necessary to inject daily per capon for five days the equivalent of 136 cc of human blood. Three different methods of extraction were employed on aliquots of the same mixture of blood with and without hydrolysis of the aqueous phase. We found four international units per liter of blood. This value does not seem unreasonable. If we assume, first, that the form

\*In these studies as well as those on the aqueous phase from testis tissue I am indebted to Messrs Walter H. Hoskins, J. Robert Coffman, and George W. Beach for valuable assistance.

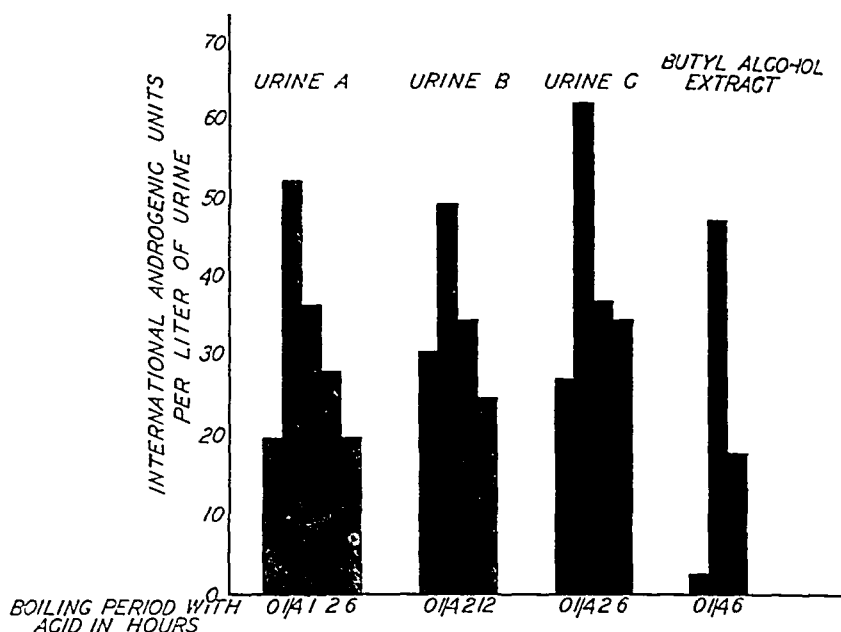


Fig 5

of androgen in the blood is testosterone, second, that testosterone is converted into androsterone before it is excreted, and third, that the rate of clearance of blood by the kidney is 75 cc blood per minute, the androgenic content of the 24-hour sample of urine should be 65 international androgenic units. The average amount of androgen in young men's urine is approximately 60 international units per 24 hours. If instead of assuming that all the testosterone is excreted as androsterone, we assume it is excreted as a mixture of androsterone and dehydroandrosterone with the activity in the urine equally divided between these two urinary androgens it would call for approximately 86 milligrams of the pure androgenic mixture. In these calculations we necessarily have made many assumptions and no claim is made as to the significance of the results. The values obtained are, however, interesting and suggestive.

*Urine* The early assays on human urine gave values of 1 to 2 capon units (not over 4 international androgenic units) per 24-hour sample. With improvement in methods the yield was gradually increased until the values accepted at present for a normal man are 40 to 100 international androgenic units per day. The increased yields are due to more efficient extraction, to preliminary acid hydrolysis of conjugated forms, and to better control of destruction by the acid subsequent to hydrolysis. The

evidence for the existence of the conjugated form<sup>20 21 22</sup> and for the acid lability of part of the free androgenic material is given in Fig 5 The first three pyramids show the effect of the length of time of acid hydrolysis at boiling temperature on the yield of androgens from raw urine The last pyramid represents the effect of acid hydrolysis of the normal butyl alcohol-soluble but benzene-insoluble fraction obtained from freshly acidified unboiled urine The urine which had been thoroughly extracted by butyl alcohol was boiled with acid and extracted with benzene in the usual way but the yield of additional androgenic material was negligible It is evident that normal butyl alcohol is an excellent solvent for the conjugated form of urinary androgens, that practically all the androgenic material in urine is in an inactive water-soluble conjugated form, that acid hydrolysis yields the free form and that prolonged boiling with acid destroys considerable of the activity which was liberated in the first fifteen minutes of boiling The conjugation appears to be of the hexuronide type The gradual loss of activity with more prolonged boiling appears to be due to the destruction of dehydroandrosterone We conclude therefore that androgens, like estrogens and decomposition products derived from progesterone, probably are excreted as hexuronides Later investigations may demonstrate varying amounts of conjugated and non-conjugated forms in blood and urine and it is easily possible that such differentiation may be of considerable significance in determining diseased conditions It may help in interpreting those cases in which abnormally high or abnormally low total values have been found without the manifestation of the expected physiological differences

With our improved methods of extraction<sup>20</sup> we have accumulated considerable data on the urinary excretion of androgens in normal and abnormal men and women, in children and in various mammals The results are tabulated below

	INTERNATIONAL UNITS PER DAY	MG EXPRESSED AS ANDROSTERONE
Men's urine (25-35 yrs )	40-100	4-10
Women's urine (23-34 yrs )	30-100	3-10
Boys' urine (6½ to 10 yrs )	0 7-2 0 liter	0 07-0 20
Girls' urine (8-10 yrs )	1 8-2 0 liter	0 18-0 20
Stallion	1-8 liter	0 1-0 8
Bull	<1 liter	<0 1
Ram	4 liter	0 4
Rat	<1 liter	<0 1

## URINARY EXCRETION OF ANDROGENS AND ESTROGENS

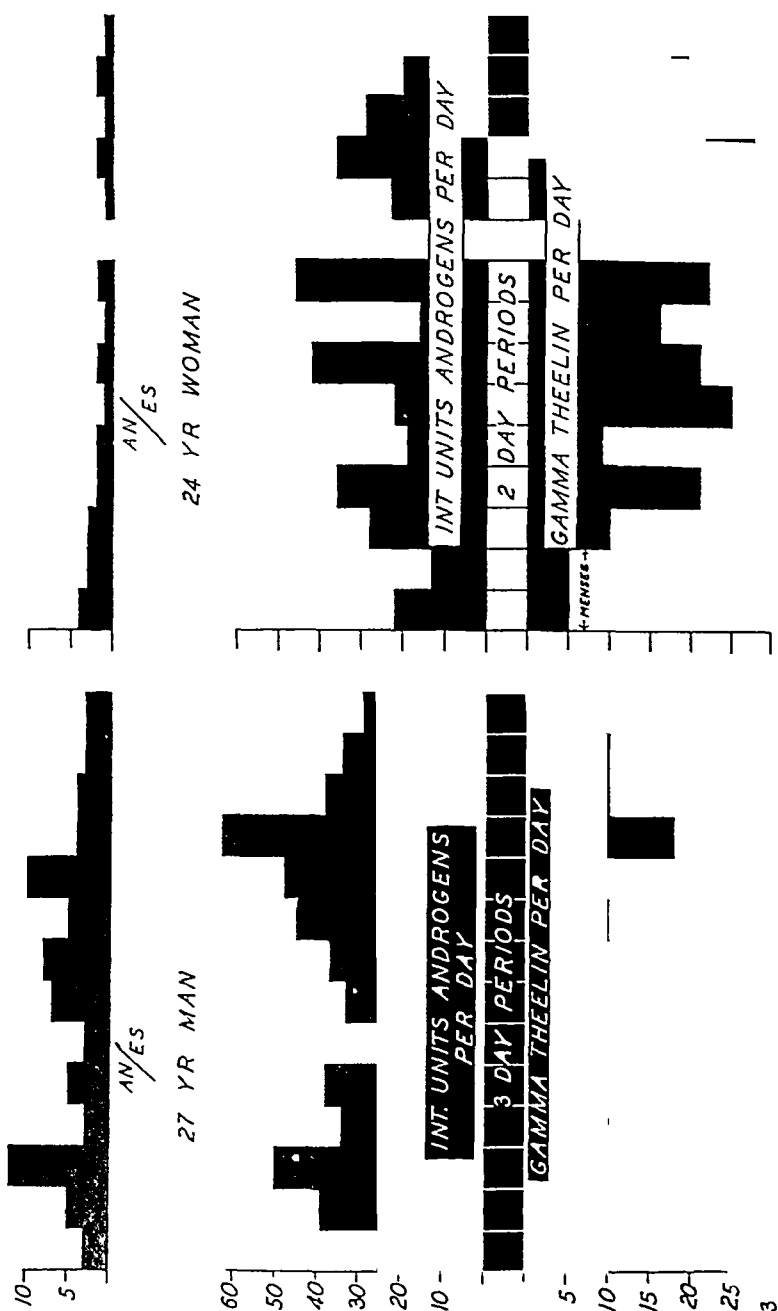


Fig 6

It is evident that the excretion is exceedingly low in humans before puberty, but that adult men and women are unique in excreting large amounts of urinary androgen. These high values are all the more startling when we recall that Butenandt first separated only 15 milligrams of androsterone from the concentrate of 24 000 liters of human urine.

TABLE IV

The daily urinary excretion of androgens and estrogens in normal men and women

"An" designates international androgenic units per day "Es" designates estrogenic activity expressed as gamma of theelin per day

SUBJECT	AGE	TOTAL PERIOD	An			Es			An/Es		
			Max	Min	Ave	Max	Min	Ave	Max	Min	Ave
		days									
1 ♂	27	42	63	24	38	18	4	9	12	3	4.2
2 ♂	26	42	65	27	41	20	2	9	22	2	4.6
3 ♂	30	44	79	13	41	29	2	10	22	1	4.1
4 ♂	35	36	65	23	40	21	5	12	6	2	3.3
Averages for men					40			10			4.1
5 ♀	34	27	42	17	25	40 <sup>a</sup>	7	27	3	0.5	0.9
6 ♀	31	30	35	18	26	60 <sup>a</sup>	13	36	2	0.3	0.7
7 ♀	24	30	46	13	28	28 <sup>a</sup>	5	18	4	0.4	1.6
8 ♀ <sup>1</sup>	23	31	85	42	56	41	4	20	11	2	2.8
Averages for women (subject 8 not included)					26			27			1.1

<sup>1</sup> In this case the urine was boiled for 15 minutes with 10 per cent HCl by volume before extraction by benzene. All other samples were boiled under the same conditions for 2 hours.

<sup>2</sup> 12th day after menses

<sup>4</sup> 20th day after menses

<sup>3</sup> 14th day after menses

<sup>5</sup> 18th day after menses

Today we should expect to find 15 milligrams of androsterone in four days' average collection of human urine. The reasons for the low yield of product by Butenandt are incomplete extraction, appreciable destruction, and the great difficulty in separating the pure androgen from the complex concentrate.

*Variations in excretion in normal men and women.* The systematic assays on complete collections of urine from men and women over periods of 27 to 44 consecutive days showed marked variations in the amount of androgens and estrogens excreted per day.<sup>20</sup> Fig. 6 shows these fluctuations in a man and in a woman. The minimum, maximum, and average values found for the four men and four women are given in Table IV. It should be emphasized that these analyses required pooling the collections into 2- to 4-day samples in order to obtain enough material for accurate assay purposes. In other words, the daily variations as given are already

averaged and therefore it is easily possible that the actual daily excretions are over a still greater range. These variations in normal men and women should serve as a warning not to place too much emphasis upon the assays on one or two 24-hour samples of urine. Furthermore such amounts of urine are of doubtful value because the assay is likely to be based on too few capons. Inasmuch as tremendous variations do occur normally it is much wiser to average these results and increase the accuracy of the assay by extracting large volumes of urine preferably representing more than 3 days' complete collection.

In studying Table 4 it should be observed that the analyses of the urine from subject 8 were carried out after hydrolyzing with acid for fifteen minutes instead of for two hours as was the case with the other seven subjects. This accounts for the high yield of androgens in this case. A number of comparative assays carried out on urines after fifteen minutes' and two hours' boiling with acid have shown that the former procedure leads to an increase of 66 per cent over the latter in androgenic units. If we assume that this increase would have been observed in the other seven subjects the average daily excretion of international units of androgens would be sixty-six for the men and forty-seven for the women and the average An/Es ratios would be 6.9 for men and 2.0 for women instead of 4.1 and 1.1 as given in the table. It appears that the sex differences in the ratios are due more to a lower excretion of estrogens than to a higher excretion of androgens in men. Attention should again be called to the striking daily variations in the An/Es ratios in each individual. In other words, there does not appear any correlation in the excretion of androgens and estrogens in men and women. However, the women always excreted the lowest amounts of estrogens during menstruation and also tended toward a lower level of excretion of androgens during this period. In the women the highest excretions of estrogens were observed on the 12th, 14th, 18th, and 20th days after the menses, but this was not uniformly associated with a rise or fall in the excretion of androgens. Although Fig. 6 suggests a definite cycle of androgen excretion in the male, this is not uniformly true.

The origin of the urinary androgenic and estrogenic substances in these normal men and women is no doubt mainly from the gonads. There is no evidence that changes in diet are likely to affect the excretion rate of the sex hormones. However, other organs and particularly the suprarenal glands may normally yield products which possess androgenic

TABLE V

*The urinary excretion of androgens and estrogens in hypogonadism*

'An' designates international androgenic units per day "Es" designates estrogenic activity expressed as gamma of theelin per day

NUMBER OF PATIENTS	TYPE	AGE RANGE	An			Es			An/Es		
			Max	Min	Ave	Max	Min	Ave	Max	Min	Ave
4	Cryptorchid	13-36	31	9	16	6	1	3	31	0.8	2.8
5	Eunuchoid	23-36	17	0	11	2	1	1.7	17	0.5	8.0
2	Castrate	21-56	3.5*	1*	2	4.5*	3*	3.8	0.8	0.3	0.5
4	Gynecomastia	15-24	37	0	15	15	5	11	2.5	1.6	2.0
4	Normal men	26-35	79	13	40	29	2	10	22	1	4.1
4	Normal women	23-34	51	13	28	60	28	27	7	0.3	1.2

\* Per liter

activity. These products may be one or more of the pure substances separated from pathological urines or they may be precursors formed by the adrenals for conversion into sex hormones in the gonads.

*Urinary excretion of androgens and estrogens in hypogonadism and virilism.* In cooperative investigations with Dr. A. T. Kenyon of the Department of Medicine at the University of Chicago we have applied our methods of assay on urines from subjects with various endocrine disturbances.<sup>23</sup> Table V presents a general summary of the results in hypogonadism in the male. In cryptorchidism we observe consistently low rates of excretion of androgens and estrogens and an average low ratio as one might expect. In eunuchoids the excretion rates are still lower with a remarkably high average ratio. In gynecomastia the androgen excretion rate is of the order observed in cryptorchidism but the estrogen excretion is more of the order found in normal men and, as a result, the ratio tends toward the normal female type. In male castrates the rate of excretion of androgens is particularly low, but the change in the rate of excretion of estrogens from the normal is not of the same order. As a result the ratio values are even lower than in normal women. In short, from these limited observations we may arrive at the tentative conclusion that the absolute amounts of androgens as well as the ratio of androgens to estrogens determine the type of hypogonadism.

Table VI presents a general summary of the results obtained in virilism. In the subjects for whom the diagnosis indicated normal adrenals, the relatively normal excretion of androgens appears to be associated with

TABLE VI

*The urinary excretion of sex hormones in virilism*

An designates international androgenic units per day    Es designates estrogenic activity expressed as gamma of theelin per day

NUMBER OF SUBJECTS	TYPE OF ADRENAL	AGE RANGE	An			Es			An Es		
			Max	Min	Ave	Max	Min	Ave	Max	Min	Ave
7	Normal adrenals	13-32	44	5	26	19	6	13	3.0	0.2	2.3
2	Adenoma	31	8*	0*	4*	10*	4*	7*	0.8	<0.25	<0.5
2	Carcinoma	16-36	480	69	—	8	—	—	60	—	—
4	Normal women	23-34	51	13	28	60	28	27	7	0.3	1.2
4	Normal men	26-35	79	13	40	29	2	10	22	1	4.1

\* Per liter

a lower level of estrogen excretion and hence a ratio approximately twice that of normal women. In the two cases of adrenal adenoma the very low excretions of androgens and an excretion of estrogens even lower than in normal men are very striking. In both cases of adrenal carcinoma the androgen excretion is remarkably increased and the estrogen excretion in the one case again is lower than in normal men and hence the very high ratio. Possibly one may conclude tentatively that in women, hirsutism is not necessarily associated with abnormally high excretion rates of androgens, but that it may also, even at very low rates of excretion of androgens, be associated with a low rate of excretion of estrogens. It is, however, also possible that androgens of different types act quite differently quantitatively in influencing hair distribution and in comb-growth stimulation respectively. It is also possible that the product responsible for some types of hirsutism may be so altered before it is eliminated by the kidneys that some of its supposed androgenic action is lost.

In summary we may conclude

- 1 That at least six androgens have been obtained in pure form from human urine and animal tissues
- 2 It is generally assumed that testosterone is the true male hormone elaborated by testis-tissue although it is possible that different species may elaborate other forms of androgens
- 3 The normal urinary forms of androgens in men are androsterone and dehydroandrosterone

4 It is generally assumed that these may be derived from testosterone

5 Androsterone and dehydroandrosterone are not excreted in the free and physiologically active form, but probably as glucuronides

6 These inactive forms are easily converted into the free androsterone and dehydroandrosterone by acid hydrolysis

7 Pure androgens have not been separated from normal women's urine, hence the exact nature is not known

8 Although quantitative studies on urines from normal and abnormal men and women reveal differences in the absolute and relative rates of excretion of androgens and estrogens the data obtained are not as striking as one might have expected

9 Androgens other than testosterone, androsterone, and dehydroandrosterone have been obtained in pure form from human urine in cases of hirsutism

10 Some of these new forms of androgens may be formed in the adrenals at abnormal rates at times

11 It is very probable that the quantitative differentiation between various forms of androgens will help to explain some of the apparent discrepancies we now observe in diagnosis and urinary assays respectively

12 Finally one probably can not apply Krogh's statement, "I do not trust my reason in physiology five minutes away from the facts" more truly in any other field in endocrinology than in the one under discussion here

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## THE MANAGEMENT OF HYPERTENSION\*

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WHEN I was invited to give this lecture on "The Management of Hypertension", I wondered whether the choice of title was a happy one, first, because there seemed to be little that one could add to what was already in the literature, and second, because no matter how much "management" one undertakes, the natural history of the disease seems to run its course undisturbed. Yet when I thought more about the invitation, I came to welcome the opportunity of crystallizing my own experience against the background of hypotheses and accepted facts relating to this syndrome. Furthermore, there is one point of view in the management which I want to emphasize, for there is little mention of it in textbooks and in the literature. I shall return to this shortly.

The so-called degenerative diseases are taking on added significance since the increase in the life span of man has been secured by decrease in the death rate due to infectious diseases. Dr. Cohn<sup>1</sup> first directed attention to the fact that the apparent rise of the death rate in heart diseases was to be accounted for by its increase in the later decades, in short, in the degenerative age-group, the individual having been spared from typhoid fever or diphtheria for instance, must eventually die, and in a great number of these, the heart finally fails. As this greater number of individuals are permitted to attain an older age and as they grow older, parts of the organism begin to break down, perhaps those parts give way first which have been subjected to injury in the individual's life history, or it may be those parts to which weaknesses may have been contributed by our forebears. The social security program indicates a burden on those in earlier decades to provide for those whom our medical progress has given added years. We are obligated, therefore, to look ahead to see how we can make this older age group useful members of society and economically self-sustaining, if possible, and at the same time guarantee

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them health during this period. In this connection hypertension is important since it is one of the forerunners of heart disease in middle and later life.

I have chosen to restrict my discussion to what is commonly called essential hypertension which I shall abbreviate further to hypertension. This designation will at least provide us with a diagnostic rubric. Moreover I wish to limit my discussion to hypertension *per se* and its consequences without considering arteriosclerosis. We observe cases of hypertension before vessel changes are detected clinically. What changes in the kidneys there may be at this stage are at present not known. After hypertension has been present for a period of time, however vessel changes occur and arteriosclerotic alterations are detectable. There are accordingly individuals in whom arteriosclerosis and hypertension are interrelated and yet another group in which they may be coincident or independent phenomena.

In the treatment of disease, we can more often make greater advances when the etiological agent or factor has been discovered. In the case of essential hypertension, the etiology is still not known. There is a variation of opinion about the criteria for making the diagnosis which is further complicated by the different levels at which blood pressure readings are made, as well as the practice of recording blood pressures with the patient sitting up and lying down. Insurance companies are keeping alive the tradition of taking 'sitting' blood pressure since their statistics have been compiled on this basis. Moreover the width of the cuff, a factor which is again receiving attention, may influence the blood pressure reading. Also different levels may be read by two observers using a stethoscope with two ear-phones. All these factors make little difference in the established, easily recognized, case of hypertension but they are important considerations in the borderline case and in evaluation of therapeutic procedures. It is apparent also that they vitiate results relating to incidence.

In most clinics, a diastolic level of 90-100 mm. of mercury is accepted as the criterion for the upper limit of normal. The practice of taking resting-lying blood pressure should be encouraged, for this postural factor can be controlled for comparison in subsequent observations. A record of the sitting blood pressure may be made as well if there is reason to have this information. It is good practice to take the blood pressure at a stated time in the course of the physical examination after

the patient is at ease, and has been lying down ten to fifteen minutes, while the examiner is proceeding with the rest of the examination. Moreover, we should seek uniformity about the systolic and diastolic levels, namely, the systolic when sounds are first heard, and the diastolic when the loud sound changes to a murmur. If this cannot be detected, the level at which sounds disappear may be read and 5 mm added to it. Hypertension should be diagnosed only after elevation of the blood pressure has been recorded on several occasions.

That the etiology of hypertension has not been solved, probably accounts for studies being made from so many points of view. Let us look into some of these, for they will give us a better understanding of what we may hope to accomplish in therapy. First, what is the incidence of hypertension in the population?

It is not a matter of surprise that our notions about this particular point are inaccurate, partly because of variations in recording but also because hypertension occurs asymptotically. It is discovered in most patients when they begin to have symptoms. In certain ones, however, it is detected in the course of examinations for life insurance, in others in the routine physical examination which a few people in the total population make use of as a health precaution, and finally, in still others who come under observation because of another malady. The reasons therefore for inaccuracies about the date of onset of hypertension, about its duration and about its age distribution are apparent. Moreover, when we come to analyze the population of cardiac clinics, it appears that these patients are not followed over as long periods as patients in the rheumatic group.

What are the estimates of the incidence of hypertension? Allan<sup>2</sup> states that 40 per cent of the population above the age of sixty years exhibits hypertension. In the available statistical data relating to this point there appears to be more or less agreement that the incidence rises gradually up to forty-five years, after which there is tremendous increase in the decade from forty-five to fifty-four years and sudden falling away after seventy years.<sup>3</sup> Approximately 60 per cent of the cases occur in the forty-five to sixty-nine year period. The steep rise occurs five years sooner in women than in men, and is roughly about twice as frequent in women as men. The age of incidence suggests involutional changes as an etiological factor.

Most investigators seem to agree concerning the hereditary back-

ground of hypertension, not alone when the analysis is made from the positive point of view of the high familial incidence of hypertension in those exhibiting hypertension, but also, negatively, when one considers the low incidence of hypertension in other familial groups.<sup>4</sup> We are too strongly convinced of this notion to have it altered by Allan's analysis purporting to contradict it.<sup>2</sup> We are all impressed by the greater number of cardiovascular accidents in hypertensive families. Hines<sup>5</sup> contributes confirmatory evidence obtained in another fashion. He made the so called cold pressure test, the rise in blood pressure when the arm is placed in cold water, in the families of hypertensives. He found that the family history of hypertensive cardiovascular disease was five times more frequent in individuals with hypertension or "hyper-reactors" than it was in those who reacted normally to the test.

The racial and environmental distribution of the disease are of interest. The infrequency of hypertension in the Chinese is an accepted fact and foreigners living in China have been found to experience lowering of the blood pressure.<sup>6</sup> In urban Japanese, however, hypertension is almost as common as in Americans and in Europeans.<sup>7</sup> Hypertension is not found in Africans in their native habitat, but it is even more prevalent in negroes in the United States than in the white population. These facts lead to the opinion that the incidence of hypertension is related to the environment in which the individual lives.<sup>8</sup>

It may be stated in passing that many hypertensives are obese, but this does not appear to be the controlling factor.

The psychologic side of hypertension, as well as the constitutional panel of hypertensive individuals, will be considered shortly.

We now come to the nature of hypertension. It is agreed that the rise in diastolic blood pressure in hypertension is a consequence of increased peripheral resistance, especially in the arterioles—the precapillary portion.<sup>9 10 11 12</sup> Whether increase in peripheral resistance is due to hormonal (including chemical) changes, or to nervous control is still awaiting solution. The observations of Prinzmetal and his co-workers<sup>11</sup> and of Pickering<sup>13 14 15 16</sup> put stubborn facts in the way of acceptance of the nervous control mechanism, and yet, on this concept depends the rationale of the surgical treatment of hypertension which is now receiving wide attention. There is a vast contradictory and controversial literature relating to the two points of view, the hormonal and nervous regulation. The carotid sinus does not appear to be implicated, since its behavior

is the same in the hypertensive as in the normal subject <sup>17</sup>

A new approach to the study of hypertension was initiated by Goldblatt<sup>18 19</sup> in the production of hypertension by renal ischemia induced by the application of constricting silver clamps to the renal arteries of dogs. The means by which rise in blood pressure is achieved under these conditions has been widely studied in the light of the nervous and chemical origin. Although the matter is unsettled, the balance of evidence, at present, is in favor of a renal-humoral nature. What the final implications of Goldblatt's highly important observations will be, as well as of those growing out of his approach, cannot be stated at present, nor is it possible to assign them a proper rôle in the interpretation of the etiology of clinical hypertension in man.

Let us inquire a moment into the pathological physiology of hypertension. Again we find that studies have been made from many points of view. And indeed this is inevitable since its effects are widespread. We may enumerate certain of them briefly. It has been found that the velocity of blood flow (measured clinically as circulation time) may be normal, or may be slightly decreased in the absence of heart failure. It is significant that it is not increased <sup>20</sup>

Steele's<sup>21</sup> observations show that pulse wave velocity is increased in hypertension, and that it is related to the diastolic level and not to the pulse pressure as was Weiss' notion <sup>22</sup>

It is well known that there are certain cases of hypertension having small hearts and others having large ones. Starr has contributed data leading to definition <sup>23</sup>. He found that those with small hearts had a smaller basal cardiac output than those with large hearts. In certain ones the cardiac output was smaller than in subjects with normal hearts. This reduced cardiac output achieves the maintenance of hypertension without increase in the heart's basal work. When the basal cardiac work is not elevated, the heart is not enlarged. When it is elevated, the amount of enlargement is closely proportional to the increased work. Therefore, cardiac enlargement is analogous to that which occurs in skeletal muscle after increased work. It appears that the failure of cases with prolonged hypertension to develop cardiac hypertrophy may be attributed to the reduced cardiac output and it has been found that they show no hypertrophy at autopsy examination. Clinically, cardiac decompensation is less likely to occur in cases of hypertension with small hearts than in those with large ones. As we have stated, the arterial pressure is increased

but the venous pressure is not elevated unless cardiac failure is present

Early, the electrocardiogram is usually normal, but later it may show certain alterations. There may be left axis deviation which will usually indicate preponderance or hypertrophy of the left ventricle. When T wave changes occur, they may be associated with the hypertension *per se* or may indicate that changes in coronary vessels have occurred.

The basal metabolic rate may be normal in hypertensive subjects.<sup>24</sup> The viscosity of the blood and the blood volume do not differ significantly from normal.<sup>22</sup>

Steele<sup>25</sup> has shown that the skin temperature of persons with hypertension does not differ from normal individuals and that variations in it occur without change in blood pressure. Elevation of blood pressure in persons with hypertension does not primarily depend then on constriction of the arterioles of the skin.

We come now to the renal physiology. The tests of renal function, namely, urea clearance, the phenolsulphonphthalein excretion, and the limits of concentration and of dilution may all be in the normal range in the presence of hypertension.<sup>26</sup> The chemical constituents of the blood, for example urea, chlorides,<sup>27</sup> and cholesterol,<sup>28</sup> may show no alteration. Nor is there indisputable evidence that this blood has unusual quantities of pressor substances.<sup>29</sup> After the persistence of hypertension, however, changes in renal function usually occur. It is not known whether there is a time factor. It has been found that the urea clearance test detects impairment earlier and is more sensitive than the others. The phenolsulphonphthalein excretion is the least sensitive test. Changes in plasma proteins, and in the red blood cell count and hemoglobin of the blood occur only late, if at all. Addis' sediment counts may at first show no alteration in the number of formed elements. Later, however, changes may be detected.

When a patient comes under observation, how can we evaluate his condition?

First. With respect to the functional capacity of the heart, the best guide is the patient's own history of how much can he do with or without symptoms, data which are best ascertained by listening to a detailed account of a day's activities, and finally what signs of failure does the patient exhibit.

Second. The following examinations aid in evaluation of the state of the kidneys: (1) the urea clearance and the blood urea, (2) the range

of the specific gravity of the urine in concentration and dilution tests, (3) the phenolsulphonphthalein excretion, if the urea clearance test is not available, (4) the sediment of the urine, and perhaps the Addis count, (5) the albumin excretion in the urine

Third Anatomical changes may be disclosed by the following procedures Examinations are made to determine the state of the peripheral vessels, the eyegrounds for vessel changes—papilledema, hemorrhages, an x-ray of the heart for its size, an electrocardiogram to discover axis deviation and coronary artery changes

Fourth The level of the blood pressure should be determined The diastolic level is the more important I prefer to see a patient with a labile blood pressure than one in whom the level is fixed It is well known that patients may exhibit for years high systolic blood pressure without revealing any of the changes mentioned above

Fifth Inquiry should be conducted to gain an insight into the personality of the patient for the help it contributes in therapeutics

The clinical course of hypertension is not accurately known because of its insidious onset without symptoms and because patients may not be observed carefully until they show evidence of strain on one of the systems

What may be the course of events in patients who exhibit hypertension? In the first place, they may live their life span and suffer an intercurrent disease In the second place, the predominant damage and strain may be cardiac from which they develop congestive heart failure The failure is occasioned in a great majority of cases by coronary artery sclerosis or it may be subsequent to coronary thrombosis Congestive heart failure is the most common cause of death of patients with hypertension From another point of view, hypertension is the most common cause of cardiac affections in persons over fifty years of age, one quarter of all deaths being due to it (Averbuck<sup>30</sup>) In the third place, as I have already mentioned, they may suffer coronary occlusion with the course of events that this implies In the fourth place, certain others suffer renal changes and renal death is their lot, and finally, others experience cerebral vessel changes and cerebral accidents

Flaxman<sup>31</sup> has analyzed a series of 623 cases, 189 of which were dead and 434 known living Eighty per cent of those who have succumbed died two years after onset of symptoms, 65 per cent of those dying, died of congestive heart failure, congestive heart failure occurred most

frequently one year after symptoms appeared and 85 per cent died one year after the incidence of heart failure, 64 per cent of negroes died before fifty years of age, but only 30 per cent of white sufferers died before fifty years of age, a few were living five to twenty years after the first appearance of symptoms, and a few were living five to eight years after onset of congestive heart failure

Patients may live many years though the systolic level is high, but the diastolic level is more important in prognosis, and lower diastolic levels favor longevity. Good renal function is a favorable sign. Moderate cardiac hypertrophy is not unfavorable, but large hearts are more likely to fail than small ones.<sup>32</sup> Women appear to tolerate high blood pressure better than men. Cerebral accidents, anginal attacks, and retinal hemorrhages are unfavorable signs.

In passing, there is one situation in which hypertension appears to be of benefit, namely, in the presence of mitral stenosis. It was Levine's and Fulton's belief<sup>32</sup> that the favorable influence on the natural history of this valve lesion is achieved by the enlargement of the left ventricle and dilatation of the stenotic ring which hypertension encourages.

I should like to discuss heart failure briefly. Hypertensive patients suffer several types of failure. First, they may experience paroxysmal rises in blood pressure, the so-called vascular crises, which may be attended by acute heart failure. Second, they may exhibit acute cardiac dilatation with pulmonary edema. Finally, they may sustain the sequence of events recognized as chronic congestive heart failure. For the relief of the first, the liberal use of morphine is indicated. It has been found that adrenalin may give them rapid relief, and results, not in further rise in blood pressure, but in its fall. Aminophyllin intravenously may be used. In the treatment of pulmonary edema, morphine is invaluable. I do not resort to venesection unless the patient's condition is very urgent. Digitalis in full therapeutic amounts is given by mouth or rectum. I do not subscribe to the use of hypertonic glucose solution, for it draws fluid from the tissues into the blood stream, adds to the volume of the circulating blood, which in turn increases the load on the heart.<sup>33</sup> Oxygen therapy may be instituted and may be given under positive pressure as recommended by Barach.<sup>34</sup>

When congestive heart failure occurs, it has the usual signs and symptoms associated with failure and needs no special comment. The changes in the circulation are similar to those occurring in patients

suffering failure from other causes, such as rheumatic heart disease, namely, decrease in cardiac output per minute and per beat, rise in venous pressure, and slowing of circulation time, and the work of the heart per beat is not commensurate with the heart size<sup>35 36 37 38</sup> The giving of digitalis results in decrease in size of the heart, increase in cardiac output, fall in venous pressure and shortening of the circulation time, and the work of the heart is increased per beat and the heart now smaller, the work is more nearly commensurate with the heart size<sup>35 36</sup> The treatment of heart failure in hypertension is the same as in other etiological types, namely, (1) the use of digitalis in full therapeutic amounts, (2) low salt diet, (3) restriction of fluid intake, (4) antihypertensive drugs, such as theocalcin by mouth, and aminophyllin by mouth or intravenously, (5) one of the mercurials intravenously may be required Mercurpurin, a mercurial combined with theophylline, has, in my experience, been the most valuable of this group for the mobilization of fluids<sup>39</sup> Renal function does not appear to be impaired by its use and it may be given if hematuria is not marked

During failure, the blood pressure rises in certain patients and falls in others and seeks its usual level as restoration of efficiency occurs Mention may be made also of the fall in blood pressure which occurs in coronary occlusion Since the blood pressure may remain low after recovery, in the evaluation of a case seen at this time, it may be helpful to ascertain the history of preceding hypertension

The symptomatology of hypertension is not clear The experience is common that patients suffer no symptoms until by chance hypertension is discovered, after which they have many complaints Moreover, what symptoms are due to hypertension *per se* and what to the "complications", are not separable from the records now in use Certain analyses have indicated that hypertensive symptoms are psychogenic in origin<sup>40 41 42</sup> The symptoms, whether related to hypertension *per se* or its complications, or whether psychoneurotic in origin, are too well known to enumerate Analysis of the symptoms, as they have been recorded in the past, does not give a clear insight into their origin and nature

We come now to the treatment of hypertension I shall speak first of drugs I am of the opinion that none of the drugs directed toward lowering blood pressure are of benefit In testing any procedure it must be kept in mind that the effects are difficult to evaluate because of expected

fluctuation in blood pressure and of relief of patients when they are given any kind of medication

Gager<sup>43</sup> has recommended the use of potassium sulphocyanate, to be given 0.1 gm three times a day after meals for one week then twice a day for one week then once every day for one week and then every day or every second day. The attempt is made to keep the level of cyanate in the blood at 10 mgm per cent, since toxic symptoms occur when it is 15 to 30 mgm (psychosis, dermatitis, cardiac pain<sup>44, 45</sup>). In certain patients, fall in systolic and diastolic blood pressure and relief of subjective symptoms occur. I have not had much success with its use.

Bismuth subnitrate may be given for the nitrite effect, in 0.6 gm amounts three times a day. Biuen<sup>46</sup> is of the opinion that it gives no greater fall in blood pressure than the usual variation which is encountered. There is danger of cerebral accidents from its use.

Erythroltetranitrate in 0.03 gm doses may be given. I have not had occasion to use it for some years.

Of the tissue extracts, lacarnol is the only one I have tested. I can attribute no significant benefit to its use.

The salt free diet has enjoyed a vogue, but too much has been claimed for it. Under well controlled conditions fall in blood pressure occurs in certain patients and they experience fewer symptoms on the regime, and are on the whole more comfortable. Universal success, however, is not to be expected. I usually follow the practice of recommending a low salt diet.

The place of luminal and barbiturates in the management of hypertension will be discussed later.

We come now to the place of surgery in the treatment of hypertension, a pertinent question at the moment. Hypertensive patients and the lay public are hearing too much about it through pseudo-scientific writings and the newspapers. It raises a hope in them which, at the present time, is not justifiable. It would be unfortunate to subject great numbers of individuals to this therapy under uncontrolled conditions until a number of well controlled cases have been observed for a sufficient time to permit its evaluation and to establish its effect on the life histories of those treated. Our analysis made in the earlier part of this discussion makes apparent the difficulties inherent in such an evaluation. Time will not permit a detailed discussion of the various surgical procedures, nor is it profitable for us in view of the fact that the part it plays at the present

time in the management of the hypertensive patient must sanely be restricted to a few selected cases. Everyone subjected to therapy should undergo thorough evaluation beforehand in the manner we have indicated. The recent literature has many papers recording the experience of those who have explored this field.<sup>47-48-49-50</sup> Dr. Heuer<sup>51</sup> has recently summarized his and Page's experience. The operation of division of the anterior nerve roots of the spinal cord from the level of the sixth dorsal to the second lumbar vertebrae level resulted in fall in systolic and diastolic levels of blood pressure, regression of retinal changes, and improvement in subjective symptoms in a sufficient number of patients to encourage this approach. In certain ones, the blood pressure rose again later. The operation itself is associated with real dangers which are cause of concern. Again, splanchnic resection in Heuer's experience was associated with fall in blood pressure, relief of subjective symptoms, and regression of retinal changes, but the blood pressure rose to the preoperative levels in all patients in six months.<sup>49</sup> Dr. Heuer and I are expanding this series of patients in order to observe further the possibilities of this procedure. Those patients who have exhibited improvement following one of the surgical procedures, encourage the continued exploration of the application of surgery to this province but what place it will eventually take and which of the procedures will prove to be the most beneficial cannot be foretold at this time. Too wide use should not be encouraged for fear it will fall into disrepute before its usefulness has been established.

How does one "take care" of a patient suffering from hypertension? Much of what we do should be directed toward an understanding of the individual who has the disease. By and large, they have increased psychomotor activity, they are dynamic hyperactive individuals; they are sensitive, quick tempered, yet they have certain differences from the manic depressive groups which they may simulate, for they are not moody and are not the "up and down" type. Ayman and Pratt's analysis shows that hypertensive symptoms are of psychic origin.<sup>42</sup> There is still the difficulty in deciding whether the patient is this type of person because he suffers from hypertension or whether he develops hypertension because of this individual type. Extensive studies have not been made to discover whether there is a constitutional panel, - morphological and physiological, of hypertension such as Draper<sup>52</sup> has described for gastric ulcer or gall bladder disease.

Since no specific drugs nor certain surgical treatment are avail-

able for the hypertensive subject, we must resort to the lines of symptomatic therapy. Having evaluated the patient's anatomical lesion and functional capacities, how do we take care of him? First, what is the general regime? (1) No special diet is indicated, but it should be a well balanced one. Protein should not be restricted, first, because it has been shown that it is not a factor in production of hypertension, and second, its limitation may lead to plasma protein depletion and favor the onset of edema. Salt may be limited to that used in cooking but highly salted foods are prohibited and highly seasoned ones eliminated. (2) If the patient is overweight, the caloric value of the diet should be reduced, without deprivation of essential factors. (3) Regular bowel habits should be established. (4) The use of tobacco should be eliminated. There is no evidence that tobacco is of benefit while there is some pointing to its harmful effects. This point of view is discussed frankly with the patients to prevent disappointment. (5) The moderate use of alcohol is countenanced because of its vasodilator effect. (6) Strenuous sports are discouraged, but the patient may indulge in less active games. Each case must be individualized. (7) Luminal is one of the most useful drugs in the care of the hypertensive individual. It is prescribed for the relief of persistent headache or to lower the level of hyperactivity. It may be given over long periods of time. (8) If hypertension has appeared at the menopause, an ovarian extract may be useful.

In the regime of persons with hypertension, the excesses should be eliminated, they must not overwork, nor overeat, nor undersleep, nor oversmoke. Measures are directed at relaxation and attaining mental ease. Part of this is secured by psychotherapy and part by re-training the patient by his own efforts. Plans should aim at lowering the pace at which the patient lives and toning down his reactions to his environment. The patient must acquire a different pattern of living. How can these objectives be attained?

First, one should try, without engendering fear, to encourage the patient to take the attitude that it is better to lead a slightly restricted life over a long period of time than incur long invalidism. Second, hot baths at home and occasional visits to Spas for the "cure" may be helpful. Whether lowering of blood pressure to the extent that is claimed at the Spas occurs, I am unable to say, nevertheless, certain patients are symptomatically benefited by the regime. Third, long hours of sleep should be indulged in. Fourth, relaxation periods during the day may be

in order Executives may have a couch in the office and lie down after lunch Fifth, frequent short vacations away from business worries may be possible Sixth, remove worries, if it is possible It may be expedient to remove certain patients from one business to a less disturbing one, or from one department to another Seventh, the organization of the home life should be scrutinized Eighth, relaxation at night without night work is essential Ninth, exposure to the hot sun should be avoided Tenth, if the patient is not aware of the rise in blood pressure, it may be best not to discuss it with him, but with a member of the family Eleventh, the patient should be reassured about his blood pressure, and given the bright side of longevity, he should be told something about the rationale of therapy Twelfth, the patient should be encouraged to acquire a hobby Finally, in the direction of psychotherapy The best results will be secured by listening to patients' troubles and, if it can be done, rearranging lives This takes a great deal of the physician's time, but it appears to me from my experience to be the best therapeutic measure we have at our disposal It is a side of the therapy that is not usually recognized, and if recognized, not given proper emphasis nor adequate attention For the most part, these patients do not need psychotherapy in the usual sense of the word, nor do they need to be transferred to the care of a psychiatrist As a matter of fact, harm may be done to certain patients if the latter course is pursued, because of the present implications to the patients of having psychiatric care, and because something is lost, so far as patient and doctor relationship is concerned, by transferring the patient from your care to someone else for this phase of therapy I should like to encourage attention to this phase of the management From the psychotherapeutic standpoint, no problem in their lives can be too trivial for them to bring to the physician, since it may be the trivial problems that they magnify into great ones Their state is very susceptible to improvement by encouragement The exacting care which this kind of treatment necessitates is hard on the physician, but is a responsibility which we must assume

On the other hand, I have emphasized that they must be encouraged to stand on their own, and they must be re-trained and induced to moderate their lives Jacobson<sup>54</sup> has made contributions in this direction by the technique which he calls "Progressive Relaxation" It has as its objective, the training of individuals to relax and to eliminate "tensions" The methods involved are somewhat too tedious for brief exposition

Careful scrutiny of his physiological studies and of the description of the techniques employed, convince me that a new approach has been opened in the therapy of hypertensive patients which has not yet been sufficiently explored. The data are described in Jacobson's monograph entitled "Progressive Relaxation"<sup>54</sup>. Patients find his volume entitled, "You Must Relax",<sup>55</sup> written for the laity, very helpful in attaining the objectives.

Some of the problems which arise may be illustrated by a case report. Mrs. A., a tall blonde woman, sixty years of age, has suffered hypertension for fifteen years. Blood pressure levels have ranged from 160/100 to 240/120. She has suffered eye-ground changes and experienced vascular crises. She is a dynamic person, whom husband and children have relied upon and looked upon as having unlimited endurance. She seems incapable of making certain decisions and the family are unable to do this for her because they are too close at hand, consequently, the patient requires an outsider to help her make up her mind and bear part of the burden of the decisions. This patient owns property which she thinks no one but she can manage. The husband's business office was in the house and it was apparent that the home-office relationship was a very disturbing factor in attaining any degree of relaxation for the patient. It was only after some while, that I succeeded in persuading the family to live in an apartment. There were conflicts because they had always lived in a house and the idea of living in an apartment did not appeal to them. The patient had to remain in her own room day after day because she was unequal to walking the stairs to the living quarter of the house. Once the decision had been made and the objective gained, the wisdom of the change was apparent. It requires constant foresight on my part to see that she does not undertake too much. She has not such a lowered reserve but that she can endure moderate activity, but her idea of a quiet day does not coincide with mine. My efforts are directed at persuading her to engage in relaxing activities rather than the worries of the household which give her concern and result in tension. I have succeeded thus far in having her take an attitude of nonchalance about things. I encourage the attitude that if she can do something about a situation, to do it, but if she cannot, let it go and not worry. But it is an attitude that needs continual encouragement to maintain. When things go wrong, there are the usual symptoms, when life is serene, she is comfortable. The level of blood pressure under these circumstances

may or may not follow the course of the symptoms. It is apparent that these patients are very susceptible to suggestions and encouragement and a well guarded word about level of blood pressure, if they happen to know about it, or an explanation for its change is helpful. Often, if you can remove the cause for the worries, the symptoms disappear. We must be careful, however, not to put too much stress on suggestion, implying a passive rôle on the part of the patients, but rather to encourage an active rôle of their own, such as is involved in the technique of "Progressive Relaxation." Striving to accomplish a task of which they are not capable and uncongenial surroundings, all contribute to the tension state. With careful guidance these may often be rationalized and altered. I have discussed this approach in every day words which may appear to be conceived or expressed vaguely. I am of the opinion, however, that we know too little about this approach, in the scheme of hypertensive therapy, to cloud it with high sounding words which would only cloak our lack of knowledge. Perhaps out of simple beginnings further progress may take place.

There has been very little conscious attention, as I have said, given to this side of therapy, although most physicians in their sympathetic attitude attain the same end. It is an admittedly laborious procedure, but one we must try, if it gives promise of benefit. Because it is time consuming, one clinic in Boston has attempted this form of treatment on a mass basis, by a class method.<sup>56</sup> They have recognized the susceptibility of these patients to suggestion and are turning it to good account. In this class, the nature of hypertension is first explained in simple terms, the rôle apprehension and worry play in it and in symptomology are discussed. In each class period the patients are taught relaxation, and practice it for a short time, and finally recognizing suggestion further, the testimony of a member is heard. Marked improvement in symptoms and in the outlook of the patients is reported to result from this form of therapy and two thirds of them have shown a fall in blood pressure.

In closing may I again say that neither the course of the disease nor its progression may be altered by these techniques, but if we make the subjects more comfortable and happier individuals, it has been worthwhile. I am afraid I have taken liberties with the title, but trust that I have given a perspective of hypertension. I trust also that I have encouraged the point of view of looking upon and of treating the individual as a whole, with attention directed to the "tension" side and to the

psychiatric approach, for symptomatic relief can be given to hypertensives by understanding them and treating them as individuals rather than as just "cases" of hypertension to be treated by drugs which prove of little benefit

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## LIBRARY NOTES

## BOOK REVIEW

*Internships and Residencies\**

This volume, which consists of an analysis of interns and residencies of 329 pages and an appendix of 148 pages (of which 15 pages are bibliography) is a tremendous piece of work.

It is almost impossible for a reviewer to give a satisfactory account of its contents, as the text is all merit and very few extra words are used. It is a study garnered from interns, attendings, ex-interns, residents and practicing physicians.

The first part of the volume under consideration is taken up by the study of the resources for intern and graduate education in New York, defining teaching hospitals, affiliated hospitals and non-teaching hospitals and defining also the terms of internship, residencies and Fellowships.

This is followed by the history and evolution of the intern and residents.

A most interesting chapter relates to a survey of a questionnaire answered by 1904 practicing physicians, graduates of New York City medical colleges who have had internships in New York. In the introduction there is a very terse statement which really expresses the purpose of this volume. It is as follows: "There has been too much interest in what the interns could do for the hospital and too little consideration to what the hospital could do for the intern."

"Advanced training, as special internships, residencies and Fellowships, have been in the experimental stage, without uniformity of plan or purpose, and the intern groups have suffered from lack of guidance, and

clearly defined objectives, and have frequently made poor use of their opportunities.

"The student period from the beginning of the pre-medical course to the end of the internship has averaged from eight to ten years. For their professional careers the demand was long and of arduous proportion, and one might expect an almost uniformly adequate medical qualification." If one follows the recommendations in this volume and the present trends in medical education this average will be increased to at least thirteen years, for the recommendation of the various combined boards demands a two-year rotating internship followed by residencies of two to five years. This means that the prospective medical student is dependent on his family until he is thirty years of age, a tremendous economic responsibility. To show the scope of this work questionnaires accompanied by personal letters were sent out in 1935 and 1936 from the deans' offices of Columbia, Cornell, Long Island, New York Medical and Flower Hospital, and New York University Medical Colleges, to 3,299 of their graduates for the years 1919 to 1921, 1924 to 1926, and 1929 to 1931. These periods were selected as giving a representative sample of graduates during the fifteen years preceding the time of the present survey. In all, the surprising number of 1904 carefully-answered questionnaires were returned for analysis. The analysis indicates where the men were practicing the type of work they were doing, and their opinions of the advantages and disadvantages of intern training.

It was found that 20 per cent of the graduates secured appointments on the staffs of teaching hospitals and 26 per cent on the staffs of hospitals with medical school affiliations. Only 12 per cent had no hospital contacts and were therefore completely divorced from

\* Report by The New York Committee on the Study of Hospital Internships and Residencies. Jean Alonzo Curran, M.D., Executive Secretary, New York. The Commonwealth Fund, London. Humphrey Milford, Oxford University Press, 1938.

the educational advantages of hospitals

The volume is replete with numerous tables of analysis of the studies, grouping the surgical and medical specialties separately

Chapter V, which is full of most valuable material, is concerned with factors contributing to house staff efficiency. This subject is taken up from the point first of physical well-being and efficiency of interns, including health care, housing, call systems, recreation, food, remuneration and uniforms. It is interesting to note that despite the risks taken by the intern on the ambulance and in the hospital he has been protected by insurance only in the rarest instances. Provisions of the State Compensation Law are inadequate when applied to interns, since interns are apprentices and not salaried employees. At the time of this survey only eight of the sixty hospitals studied were making a routine health examination of their interns. The importance of reexamination every six months the committee feels cannot be over-emphasized. The living quarters provided for interns and residents have been inadequate, according to this report, in over half the hospitals of New York City.

There is an excellent chapter on hospital libraries and the use of these libraries. It has been found that the interns are stimulated to reading largely by the attending staff and also it has been found that a resident librarian is necessary in order to have the library properly protected.

A very interesting and important subject considered is the introduction of the intern to the hospital. The first hours of an intern after his entrance into a hospital may influence his entire hospital career. If the seniors on the staff have a pessimistic attitude toward the hospital and toward the attending staff his reaction is apt to be influenced. In the reviewer's experience it took three years to change the morale of a hospital staff so that it became loyal supporters of a new regime. The committee believes that a member of the attending staff should be assigned for the instruction of each intern entering the hospital. Where this is impossible manuals and procedure books presented to each intern on admission have proven satisfactory. A voluminous manual, however, has frequently prevented

the intern from mastering its contents. The committee recommends a hand-book containing merely the outline of the hospital's methods in current use. This book must be revised every few years in order to prevent its becoming obsolete. The following subjects are considered necessary for such a manual:

- 1 Organization of the house staff, with an outline prescribing the duties of each member
- 2 The relationship of the intern to the hospital administration, attending, nursing, social service, and technical staffs
- 3 Attitude toward patients
- 4 Outline for record of the history, physical examination, progress notes, and case summaries
- 5 Special diagnostic and therapeutic techniques
- 6 The handling of emergencies
- 7 Laboratory procedures
- 8 Nursing techniques
- 9 Social service utilization
- 10 Diets
- 11 Operating and delivery room methods
- 12 Methods of securing consent to necropsy

The committee states "With or without an intern bible there has been no satisfactory substitute for painstaking teaching and supervision of each new staff member."

Chapter VIII is largely concerned with the most important subject of the entire volume—the dividing of hospital services. In this a thorough study of the rotating or straight service is analyzed, and the committee recommends that the fundamentals of an internship preparing for general practice should consist of rotation through medicine, surgery, gynecology and obstetrics, and pediatrics. It was felt that during a two-year experience the time allowance for each of these services should not be less than the following:

- Medicine — six months
- Surgery — six months
- Gynecology and obstetrics — three months
- Pediatrics — three months

They conclude that the quality of service and

incidentally the educational benefit to the intern are in most instances directly proportionate to the time spent on the service. This applies to the mixed and straight, as well as rotating internships. While the duration of each block of assignment is only one factor in producing a high grade of internship, it is manifestly an essential ingredient in a successful formula.

In studying the case load and the size of the intern staff the committee states that in general the hospitals with services of acute conditions show the best quality of medical attention and intern teaching when they had census loads of ten to fifteen patients per house staff member. It was observed further that ratios above fifteen acute cases per man were prejudicial to quality of medical service and intern instruction. This was specially evident in the hospital where the ratio rose to twenty to thirty per intern.

In an analysis of internships it was found that the greatest shortcomings in teaching were, first the instruction in such diagnostic and therapeutic methods as venipuncture, paracentesis, spinal tap and examination of body orifices. In less than one-third of the hospitals has such instruction been systematically provided. The average intern completing his service seems to be incompetent in examination of the ear, nose and throat, pelvis, anus and rectum. The second fundamental deficiency is the time allotted to the out-patient department. It is well known that the majority of cases appearing in the office of the young practitioner are the types of cases seen in the out-patient department.

The chapter on residencies and fellowships is splendidly presented but space will not allow an adequate description of this chapter. It is discussed under the following subtitles: Duties and opportunities of the resident, advantages to the hospital of a resi-

dent staff, distribution of residencies by specialty, length and plan of the residencies, evaluation of residencies as adequate training, attitude of staff members and others toward residencies and the opinion of interns. The committee believes that there should be an internship of at least two years before the beginning of a residency in any of the specialties, and the conviction of the committee is that a residency experience of less than two years is an inefficient arrangement both for the hospital and as a training experience. The committee strongly recommends in this study the necessity of out-patient department experience. A summary of the various types of residencies in the medical and surgical specialties is inadequately discussed, with the demands of the various American boards of specialties. In summarizing the residencies in the different types of hospitals and services the committee states that it has been found that residencies elevate the quality of medical service in the hospital and improve the teaching given the interns and medical students. Moreover the residencies provide an excellent opportunity for original investigation, for correlating the training in the basic sciences and for grounding in the essentials which must be included in the specifications of a specialist.

In concluding an analysis of this volume the average practitioner who is head of a hospital service is impressed with the idealization presented by the committee and the necessity for revising his own hospital service. Unfortunately, if he should live up to all of the requirements of this volume he would have to limit his private practice in order to put almost full time on teaching of interns and residents.

I should advise every chief of a hospital service to read this volume.

F W B

## RECENT ACQUISITIONS

"Possession does not imply approval"

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- Tuberculosis and leprosy, the mycobacterial diseases* Editor F R Moulton  
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## IN MEMORIAM

### EDWIN BEER

1876 - 1938

When Edwin Beer died on August 13, 1938, at the age of 62 years, the medical profession lost a man of integrity and distinction, a trusted leader, a clear thinker, loyal to his professional obligations, to family and to friends.

He was born in New York City, where he was graduated B A from Columbia College in 1896, and received, in 1899, his medical diploma from the College of Physicians and Surgeons. After serving his internship at the Mount Sinai Hospital he studied abroad, at Berlin, Vienna and Prague and, on his return, resumed his association with the Mount Sinai Hospital and was also connected with the staffs of the Lenox Hill and the Flower Hospitals. He established the cystoscopic clinic at Lenox Hill and thus early attested his interest in what was to be his chosen specialty. His association with the Mount Sinai continued until his death. He was attending surgeon from 1910 and served as president of the board with distinction.

The soundness and the breadth of his interest in fundamental medical problems as well as those of the practitioner is attested by the scope of his medical writings and by the basic sanity that characterized them. His first papers, published in 1904, five years after graduation, were entitled "Adrenal Rests in the Liver" and "Diverticula of the

Intestine. Thereafter for a number of years he was inclined toward neurological surgery and was attached to the Neurological Institute but, in 1910, when he assumed charge of a service at Mount Sinai he definitely asserted his interest in urology and in this same year he achieved the physical treatment of bladder tumors with the Oudin high frequency current, introducing, for the first time, a practical therapy for the most frequent type of bladder neoplasm, the papillary tumor. This therapy has revolutionized the treatment of bladder tumors. His monograph on Tumors of the Urinary Bladder was published in 1935. This great work was recognized first by the International Society of Urology through the initial award of its Gold Medal for service to urology to Dr Beer, in 1927, and again by the award from the American Congress of Physical Therapy, of its Gold Key, in 1937.

His other outstanding contribution to urology was the perfection of the first practical cystoscope for children, experience with which authorized the publication, in 1930, of his monograph on "Diseases of the Urinary Tract in Children", the first extensive investigation of this subject to appear in print.

He was, at various times, president of the Medical Board of Mount Sinai Hospital, president of the New York Surgical Society and vice-president of the Academy of Medicine. He served during what we have not yet learned to cease calling the World War as Lieutenant Colonel in the Medical Corps,

U S Army In the last year of his life his friends at the Mount Sinai Hospital instigated and surgeons, pathologists and urologists from the world over contributed to a *Festschrift* in his honor

This was a man as straight and true in his professional as in his personal relations, the good physician Throughout his life his profound interest was in his profession The constant application of his clear mind developed in him both judgment and wisdom He put up with no shams and thus gathered around him a group of devoted followers and students To his hospital, to the Academy while an officer, and to his students and assistants, in particular, he was always the patient, loyal friend and lucid teacher

Honesty, a devoted diligence, surgical skill, a fearless and a lucid and inquiring mind, these were his attributes He will indeed be missed

EDWARD L KEYES

## FREDERICK TILNEY

1876 - 1938

With the death of Dr Frederick Tilney on August 7, 1938 there passed one of the leaders of American medicine who did much to shape the form of Neurology not only in New York City but in the Nation Dr Tilney's career was a typical American one in that all that he received of honors and affection he earned by his hard work and his rigid scientific honesty

Dr Tilney was born into a cultured family in Brooklyn on June 1, 1876 After being graduated from the Brooklyn Polytechnic Institute in 1892 he entered Yale University where he was graduated in 1897 with the degree of A B At first he tried newspaper work on the old "New York Sun" but soon he decided that medicine was to be his field At the Long Island College of Medicine he worked and played with an exceptional group of classmates, many of whom later also made their mark in the medical world These friendships, which lasted till his death, surely helped to form that medical mind that later was to be the greatest leader of them all After his graduation from the Long

Island College of Medicine in 1903 he served an internship in the Kings County Hospital and then started his practice of medicine in Brooklyn

From the start his interests were in research as well as practice and never in his life did he get too busy with practice to neglect his research work

In 1906, with a problem of the hypophysis on his mind, he applied to Dr T Mitchell Pruden at the College of Physicians and Surgeons for facilities to work Thus began an affiliation with P & S which was to last for over thirty years After a year in Dr Pruden's laboratory he transferred his activities to the Anatomical Laboratory of Dr George S Huntington Here Tilney first really found himself Dr Huntington was a scientist of his own stamp, fearlessly honest, hard working and as sceptical of himself as he was unsparing of his time and energies A deep and lasting friendship grew steadily between these two men who were alike in so many ways Probably New York has seldom seen a personal and scientific friendship that was as intense and as lasting as that one Only those who worked with Dr Huntington know just what that means

Under Dr Huntingtons stimulus Dr Tilney naturally followed the path of his greatest interest in life—the nervous system He had written on the nervous system before and he only followed his own bent First as instructor of anatomy he taught embryology, cranial morphology and neuro-anatomy both at Columbia and at his medical Alma Mater In 1914 he was appointed Associate Professor of Neurology at the College of Physicians and Surgeons and in 1915 was made Professor of Neurology and head of the department and there he remained until his death

The history of Tilney's development of the Department of Neurology in P & S is an interesting story It was a small department when he took it over and under his hand it became a major one Neuro-anatomy and neuropathology were joined with clinical neurology to form this new department While formerly only clinical neurology was taught and that only to third and fourth year students, gradually the others fell into line until finally the department was teaching neurology from the ground up in all the four years of the medical course The Neuro-

logical clinic at the Vanderbilt Clinic was built up at the same time and by the same methods of careful, conscientious, honest work. For a number of years he worked in the clinic every afternoon seeing patients, directing treatments, and teaching. This devotion to his department rapidly drew to him the kind of assistants he liked to have. The department has always been his department.

In 1919 Dr. Tilney was appointed to a service in The Neurological Institute of New York. Ten years later the Neurological Institute merged with the Department of Neurology at Columbia University and the two moved up-town together to the new Neurological Institute building in the Columbia-Presbyterian Hospital Medical Center. The credit for that move is largely Dr. Tilney's.

The fall of 1924 saw his first and only set-back. He was stricken with right hemiplegia and aphasia. Such a blow would have finished the career of a lesser man. His come-back from that catastrophe was a source of enthusiastic inspiration to all his friends. Never did he think himself defeated but always he fought his way back. First he got back his speech and with it his old command of beautiful English and his oratory. He learned to walk again with hardly a limp and he learned to write with his left hand. He learned to get help from others in purely mechanical procedures and his research work and practice went on at a tempo not diminished. Four years after his illness he published his monumental work "The Brain from Ape to Man" which has taken a high place among the scientific publications of neurology and comparative anatomy.

After Dr. Tilney moved from Brooklyn to New York in 1917 his influence grew. His large busy private practice made great inroads into his time but never so much as to wear him away from his first love, neuro-anatomical research. Tilney was of the type of the old fashioned research man. Dr. Huntington was ever his model. Tilney, like his preceptor, knew tissue intimately. He knew from personal experience the preparation and staining of brain sections. In his early years he did it all himself but later, when time was pressing, he had to have technicians to do this work for him—tech-

nicians whom he trained and taught the work that he knew so well. At his death he was still working on the hypophysis.

Recognition came early to Dr. Tilney and came to him all the rest of his life. He was secretary and treasurer of the Brooklyn Neurological Society 1907 and 1908 and president 1911 and 1912, President of the New York Neurological Society 1917, Secretary-Treasurer of the American Neurological Association 1917-1925 and president 1926, one of the founders of the Association for Research in Nervous and Mental Diseases and of the New York Society for Clinical Psychiatry. When the Archives of Neurology and Psychiatry was established in 1919 he became one of the editors and retained that post till 1934. He founded the Bulletin of the Neurological Institute and always directed its editorial policies. His interest in the New York Academy was always one of his first. He was vice-president of the Academy from December 1931 to December 1933. In 1935 he was elected a trustee and served until his death. Besides the societies mentioned he was also a member of the American Psychiatric Association, The New York Psychiatric Society, The Galton Society, The Association of American Anatomists, The Philadelphia Neurological Society, The Royal Society of Medicine, London and the Society of Psychiatry and Neurology of Vienna. Besides these he served as Medical Director of the New York Neurological Institute 1935 to 1938 through a trying period of its career. In 1912 Columbia University awarded him the degree of Ph.D. and in 1929 the honorary degree of Sc.D.

Dr. Tilney's influence was great and probably its most lasting effects are seen in the stimulus he gave to younger people to work in scientific medicine. All who worked with him felt the impetus of his enthusiasm and the reward of his approval. His friends remember him for many things and one of those which no one could forget was his laughter. With a fine sense of humor he loved a joke and a good story. He enjoyed laughter and when he laughed he did so, as he did everything else, with his whole being. Every fiber of his big robust frame seemed to enter into his laughter and he gave himself completely to the enjoyment of it. Probably only

a man who could laugh like that could have risen above hemiplegia and after it had tried to strike him down have done the best and most enduring work of his career

The stimulus of his energy and his personality the honesty of his research work and his reporting of it the sincerity of his devotion to neurology and his teaching the charm of his culture and his friendship blended to form the Fred Tilney his friends loved All these we shall miss over the years that are to come

LOUIS CANAMATOR

### DEATHS OF FELLOWS

BEER, EDWIN 45 East 85 Street New York City born in New York City, March 28 1876, died in New York City August 13 1938, received the degree of Bachelor of Arts from Columbia University in 1896 and graduated in medicine from the College of Physicians and Surgeons, Columbia University in 1899 elected a Fellow of the Academy December 7, 1905

Dr Beer was elected a Vice-President of the Academy December 1928 and served until December 1931

Dr Beer, who was a former Chairman of the Medical Board of the Mount Sinai Hospital, was attending surgeon to this institution He was consulting surgeon to the Bellevue Hospital

In 1927 Dr Beer received the first gold medal of the International Society of Urology at Brussels The honor was for his 'original work on the application of high frequency current for the curing of intra-vesicular diseases' He held certificates from the American Board of Urology and the American Board of Surgeons

Dr Beer was a member of the American Urological Association, the American Surgical Association, the New York Pathological Society, the New York Surgical Society and one of its former presidents, the Clinical Society of Genito-Urinary Surgeons and

the County and State Medical Societies He was a Fellow of the American College of Surgeons and the American Medical Association

FRANK ALEXANDER 153 West 11 Street, New York City born in Nova Scotia 1869 died in Beechurst Long Island, New York September 18, 1938 graduated in medicine from Dalhousie University Medical College Halifax Nova Scotia, in 1897 elected a Fellow of the Academy April 1 1920

Dr Frisier who was a former professor of pathology at New York University and Bellevue Medical College, was pathologist to the St Vincent's Hospital and consulting pathologist to the New York Foundling, Peoples, Polyclinic and Mammouth Memorial Hospitals He was a Fellow of the American Medical Association and a member of the Harvey Society, the New York Pathological Society and the County and State Medical Societies

SENIOR HAROLD DICKINSON Salsbury Cove, Maine born in Croydon England, October 30 1870 died in New York City August 6, 1938 graduated in medicine from the Royal College of Physicians and Surgeons in 1892, received the degree of Bachelor of Medicine from Durham University in 1895 and Doctor of Science from Syracuse University in 1910, elected a Fellow of the Academy April 20, 1911

Dr Senior was house surgeon and physician to the Charing Cross Hospital London, 1892-93 assistant demonstrator of anatomy at the Charing Cross Hospital Medical School, 1894-95, demonstrator of anatomy at the Medico-Chirurgical College in Philadelphia, 1902-04 associate in anatomy at the Wistar Institute of Anatomy and Biology, 1904-07, professor of anatomy at Syracuse University 1907-10, and professor of anatomy at New York University, 1910-36 when he was designated professor emeritus of that institution

Dr Senior received from Durham University in 1918 the award of an honorary degree and designation as the institution's gold medalist for the year For many years Dr Senior was an associate editor of the American Journal of Anatomy

He was a Fellow of the American Association for the Advancement of Science and a member of the Anatomical Society of Great Britain and Ireland

SCHWELTZ, GEORGE EDWARD de 1705 Walnut Street, Philadelphia, Pennsylvania, born in Philadelphia, October 26, 1858, died August 22, 1938, graduated in medicine from the University of Pennsylvania in 1881, elected in Honorary Fellow of the Academy, November 18, 1926

Dr de Schweinitz was professor of ophthalmology at Philadelphia Polyclinic 1891 to 1894 and at Jefferson Medical College 1892 to 1902. He taught at the medical school, Pennsylvania University, from 1902 to 1924 and at the Graduate School of Medicine from 1924 to 1928. He was vice-president of the Pennsylvania Institute for Instruction of the Blind, a trustee of the University of Pennsylvania, a Fellow of the American Medical Association and its President 1922-1923, a Fellow of the American College of Surgeons, a member of the American Ophthalmological Society and its President in 1916, a member of the American Academy of Ophthalmology and Otolaryngology and a member of the Philadelphia Medical, Neurological and Pathological Societies. He also was a member of the American Philosophical Society, the Ophthalmological Society of the United Kingdom, the Societe Francaise d'Ophtalmologie and the Societe Belge d'Ophtalmologie.

When the United States entered the World War, Dr de Schweinitz received a commission in the Medical Corps and served in the American Expeditionary Force in France as consultant in ophthalmology, reaching the rank of Colonel prior to the Armistice and subsequently, Brigadier General in the Reserve Corps. He was member of the Editorial Board of the Medical and Surgical History of the World War. Dr de Schweinitz wrote many books and articles on ophthalmological and neurological subjects.

The degree of Doctor of Science was awarded him by the University of Michigan in 1922 and Harvard University in 1927. He held a certificate from the American Board of Ophthalmology.

Dr de Schweinitz was the recipient of the Howe prize medal in ophthalmology in 1927, the Huguenot Cross in 1928, and the Leslie Dutton medal for work in the prevention of blindness in 1930.

TILNEY, FREDERICK 920 Fifth Avenue, New York City, born in Brooklyn, New York, June 4, 1876, died in New York City, August 7, 1938, received the degree of Bachelor of Arts from Yale University, New Haven, Connecticut, in 1897, graduated in medicine from the Long Island College Hospital in 1903, received from Columbia University the degree of Doctor of Philosophy in 1912 and the honorary degree of Doctor of Science in 1929, elected a Fellow of the Academy October 7, 1915.

Dr Tilney served the Academy as a Vice-President from January 1932 to January 1934, and as a Trustee from January 1936 until his death.

Since 1935 Dr Tilney has been Medical Director of the Neurological Institute, after having been for several years chairman of the Institute's Committee on Medical Research. He was also professor of neurology and neuro-anatomy at Columbia University, College of Physicians and Surgeons, and consulting neurologist to the Presbyterian, Roosevelt, Brooklyn, Methodist Episcopal, Babies and Greenwich Hospitals.

Dr Tilney was a Fellow of the American Medical Association and a member of the American Neurological Association, the American Psychiatric Association, the Association for Research in Nervous and Mental Disease, the American Association of Anatomists and the State and County Medical Societies.

TOREK, FRANK JOHN ALBERT 108 East 82 Street, New York City, born in Breslau, Germany, April 14, 1861, died in Vienna, September 19, 1938, graduated in medicine from the College of Physicians and Surgeons, Columbia University, in 1887, elected a Fellow of the Academy January 15, 1891.

Dr Torek was consulting surgeon to the Lenox Hill and Post-Graduate Hospitals. He was a Fellow of the American College of Surgeons and the American Medical Association.

cation, a member of the American Association for Thoracic Surgery and a former president, the American Surgical Association and the County and State Medical Societies.

WHEELER, JOHN MARTIN 635 West 165 Street New York City, born in Burlington Vermont, November 10 1879 died in Underhill Center, Vermont, August 22, 1938, received from the University of Vermont the degree of Bachelor of Arts in 1902, Doctor of Medicine in 1905 Master of Science in 1906 and the honorary degree of Doctor of Science in 1928. He also received the honorary degree of Doctor of Science from the Middlebury College in 1933.

Since 1928 Dr. Wheeler was professor of ophthalmology at Columbia University and director of the Eye Institute of the Presbyterian Hospital. He was consulting ophthalmologist to the Reconstruction and a unit of the Post-Graduate Hospitals. He was

consulting ophthalmological surgeon to Bellevue Sloane, Neurological Institute Psychiatric Institute Babies, Hackensack Hospital of New Jersey and St. Luke's of Newburgh.

Dr. Wheeler held a certificate from the American Board of Ophthalmology and was a Fellow of the American College of Surgeons and the American Medical Association and was a member of the American Ophthalmological Society the American Academy of Ophthalmology and Otolaryngology and the State and County Medical Societies.

Dr. Wheeler received the Leslie Duna gold medal in 1936, awarded by the National Society for the Prevention of Blindness for his "outstanding achievement in the prevention of blindness and the conservation of vision."

He contributed many articles on diseases of the eye.

## ANNOUNCEMENTS

When in 1928 the Academy was fully established in its new home and had at its disposal additional space and funds in connection therewith, the Council authorized the President to appoint a special committee to consider expansions of Academy activities thus made possible. This committee submitted a comprehensive report which received the approval of the Council in April 1929, at which time the report was published and made available to the membership. The administration, during the intervening nine years has endeavored to carry out the broader policies adopted by the Council. As a result, the Academy has become an institution of great influence, to which many agencies in the fields of medical education, public health and social welfare appeal.

Inasmuch as these policies not only involve considerable expenditure of time and of money, but also because a gradual extension of the field of interest of the Academy has occurred, it now seems advisable that all of the activities of the Academy be again reviewed and carefully reconsidered in order to determine the relative value of each and its place both in the programme and in the financial budget of the Academy.

Toward this end a second Committee on Activities has been appointed by the Council and is now at work upon the subject.

It is important that as far as possible the officers of the Academy know the views of

the Academy membership as individuals. For this purpose the Council cordially invites the Fellows and Members of the Academy who so desire to express an opinion upon the general principles involved and the details of the programme.

Communications may be addressed to Dr. George Baehr, Chairman of the General Committee, or to any of the following Chairmen of the Reference Committees at the Academy building, care of the Director's office:

Dr. Samuel A. Brown, Chairman Reference Committee on Administration

Dr. Arthur F. Chase, Chairman Reference Committee on Sections and Scientific Meetings

Dr. Rufus I. Cole, Chairman Reference Committee on Library

Dr. Herbert B. Wilcox, Chairman Reference Committee on Medical Education

Dr. DeWitt Stetten, Chairman Reference Committee on Public Health Relations

Dr. I. Ogden Woodruff, Chairman Reference Committee on Medical Information Bureau

Dr. Frederic Sondern, Chairman Reference Committee on Miscellaneous Items

Signed for the Committee

JAMES ALEXANDER MILLER,  
*President*

LEWIS FRISSELL,  
*Secretary*

## CHANGE IN SUBSCRIPTION RATE

Subscribers to the Bulletin of The New York Academy of Medicine are advised that the Council of the Academy has authorized a

change in the subscription price for this Journal, from two to three dollars a year, effective January 1, 1939.

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BULLETIN OF  
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OF MEDICINE



DECEMBER 1938

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ADDRESS OF WELCOME  
ELEVENTH ANNUAL GRADUATE FORTNIGHT\*

JAMES ALEXANDER MILLER

President The New York Academy of Medicine

It is a pleasure and a privilege to welcome the participants in this, the Eleventh Graduate Fortnight held under the auspices of The New York Academy of Medicine

The subject selected this year, "Diseases of the Blood and Blood Forming Organs," is one of unusual interest. It is fascinating in the variety of conditions which it includes, exciting because of the brilliant advances in our knowledge which have occurred in some directions, and yet, also mysterious and baffling because of the unresolved problems which surround the subject.

All this makes the matter one of live interest to all thinking physicians, whether their interest be mainly from the clinical or from the research and theoretical side.

The program which is offered to us is extraordinarily attractive and we are greatly indebted to the Committee in Charge whose unremitting efforts have made such a splendid program possible.

We are, of course, under great obligations to the lecturers who are reporting to us on their scientific and clinical observations, as well as to

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\* Delivered October 24 1938

the clinicians in the hospitals who are offering to us the opportunity to study these clinical problems at first hand

In addition, the scientific exhibit of this year is of special interest and well deserves careful study

Altogether it would appear that this symposium is one that it would be difficult to excel

There is one additional and important factor in the situation which I should like to emphasize, and that is that in this field, as in many others, the basis of the successful treatment of the patient rests upon careful scientific research. The great progress that has been made in this field has been due to the unremitting labor of numerous workers carrying out their investigation under great difficulties. It is, I think, only proper to emphasize the fact that this progress would have been absolutely impossible if it had not been for the use of animals in experimental researches. From the time of Harvey down to the present, advances in our knowledge concerning the blood have been made possible through animal experimentation. This has laid the foundation for scientific knowledge and thus has made possible suitable treatment which has saved many lives.

It perhaps would not be one of the least of the benefits resulting from this symposium if, on the part of the general public as well as of the medical profession, there came a better appreciation of this fact and of the absolute dependence of further medical progress upon continued scientific research through the use of properly controlled animal experimentation.

REMARKS ON THE DIFFERENTIAL DIAGNOSIS  
AND TREATMENT OF PERNICIOUS ANEMIA\*

CYRUS C. STURGIS

SINCE the introduction of the modern methods of treating pernicious anemia, with their strikingly beneficial effects, one need not dwell upon the importance of recognizing the condition at the earliest possible moment. To overlook the diagnosis of a disease for which effective control methods are available, is obviously a regrettable error. In the eighty-nine years since Thomas Addison first described the disease, our diagnostic methods have improved to such an extent that pernicious anemia should be easily recognized in almost every case. In fact, with proper study, it is doubtful if there is any other disease in which the diagnosis can be made during life with a greater degree of accuracy. It is possible to go further and state that the clinician, having the advantage of a therapeutic test and repeated blood examinations during life, can surpass the pathologist in the accuracy of the diagnosis in this disease. This is because there are so many diagnostic features which are present with a great degree of constancy. In general, it may be said that if any person of middle age complains of the symptoms common to all the anemias, such as dyspnea, palpitation, recently developed pallor, weakness and ease of fatigue, and in addition has an achlorhydria, paresthesia of the hands and feet, and recurring attacks of glossitis, the diagnosis is indicated, even before the blood is examined.

After considering carefully the evidences of the disease in approximately 1,000 patients whom we have observed during the past eleven years at the Simpson Memorial Institute, it is clearly apparent that there are at least seven cardinal points of fundamental diagnostic significance. These are usually recognized or eliminated without difficulty, and, if all or even a majority of them are present, then the diagnosis of true Addisonian pernicious anemia is at once established. These are (1) Achlorhydria, (2) Macrocytosis, (3) High color index, (4) The re-

\* From the Thomas Henry Simpson Memorial Institute for Medical Research, University of Michigan. Delivered October 24, 1938, in the Eleventh Annual Graduate Fortnight.

sponse to potent anti-pernicious anemia therapy, (5) Paresthesia, (6) Glossitis, (7) Leukopenia, or the absence of leukocytosis Each of these will be discussed briefly

1 *Achlorhydria* There is no other finding, in any other recognized syndrome which occurs with greater constancy than the absence of "free" hydrochloric acid in the gastric secretions of patients with pernicious anemia Moreover, all evidence indicates that this condition has always been present in these patients, and that it will invariably remain, regardless of treatment or the disappearance of symptoms referable to the gastrointestinal tract The presence of hydrochloric acid in the gastric secretion, therefore, should eliminate at once the diagnosis of Addisonian pernicious anemia In the entire field of clinical medicine there is no diagnostic fact which can be stated with a greater degree of finality The question will at once be raised regarding those exceedingly rare instances in which it is reported that a patient supposedly had pernicious anemia but did not have an achlorhydria The answer to this is, first, such an exception is one in many thousands and from a practical standpoint, therefore, it is not of clinical importance Second, a technical error might well explain the discrepancy And, third, the patient may have some other cause for the macrocytic anemia, such as sprue, disturbance of the gastrointestinal tract including liver disease, or one of several others Finally, it should be stated that any conclusion regarding the state of the gastric juice should be based only upon observations made after the injection of histamin, which is the most powerful stimulus to gastric secretion known at present This is emphasized because a patient may be suspected of having pernicious anemia and an absence of hydrochloric acid has been noted following the use of one of the several test-meals which have been utilized as diagnostic procedures for many years More than once it has been possible to demonstrate the presence of hydrochloric acid in such patients when histamin has been used as a stimulus to gastric secretion

2 *Macrocytosis* All observers are in agreement that when an anemia is present, a macrocytosis is the most characteristic finding in the peripheral blood in patients with this disease Moreover, this is the first characteristic change to occur when the anemia develops and the last to disappear when the blood approaches normal By a macrocytosis is meant a mean corpuscular volume which exceeds 96 cubic microns and in some instances may be as great as 140 cubic microns The actual

volume of the erythrocytes is the most satisfactory evidence of the presence or absence of a macrocytosis although satisfactory information may be obtained from measurement of the diameter of the cells by the Price-Jones technic. By this method it is possible to demonstrate in a macrocytic anemia, that a majority of the cells have a diameter exceeding the average normal measurement of 7.5 microns. It should be appreciated that the level of the erythrocyte count bears some relationship to the degree of macrocytosis. In general it may be said that its degree diminishes as the red blood cell count approaches normal, and that it is more pronounced as the anemia becomes more severe. An exception to this general statement is usually noted when the erythrocyte count falls to a million or less per cubic millimeter. Although the mean corpuscular volume may then be increased, the degree of this change may not be marked, possibly because fragmentation causes the appearance of many small erythrocytes which tend to reduce somewhat the average cell volume.

It is, of course, well known that macrocytic anemias occur which are due to causes other than those responsible for the production of pernicious anemia. Such an anemia may be present in

1. Certain disorders of the digestive tract, such as gastric resection, "short circuiting" operations on the intestines or intestinal stenosis, liver disease, idiopathic steatorrhea, *Dibothriocephalus* infestation, and, chronic diarrhea due to various causes.

2. In association with various types of lymphoblastomas such as aleukemic leukemia and Hodgkin's disease.

3. In certain other anemias, as aplastic anemia, chronic hemolytic anemia, anemia of nephritis, anemia of pregnancy, and for a short interval following acute hemorrhage.

4. In myxedema.

5. In sprue and pellagra.

From a consideration of the above numerous causes of a macrocytic type of anemia, it is obvious that the presence of a macrocytosis is certainly not diagnostic of pernicious anemia. On the other hand, if a patient who is suspected of having pernicious anemia, is found to have a microcytic type of anemia, it is *exceedingly strong but not conclusive evidence* against Addisonian pernicious anemia. It should be remembered that a microcytic anemia may occasionally occur in pernicious anemia but in those rare instances when it is present, there is always some complication, the most common being hemorrhage, chronic infection, endocrine dis-

orders, or a dietary deficiency

3 *Color Index* What has been said about the macrocytosis in pernicious anemia from a diagnostic standpoint applies almost equally well to the color index which is usually 1.0 or greater. This is because there is a rough parallelism between the height of the color index and the size of the red blood cells. In general, it may be said that when they are largest, the color index is highest, and when they approach normal in size, the color index falls to approximately 1.0. In pernicious anemia during relapse, therefore, a color index of 1.0 or greater is to be expected. It is less than this only (1) At the beginning of a spontaneous or therapeutically induced remission, when the red blood cells increase at a more rapid rate than the hemoglobin, and the color index, therefore, falls to 1.0 or lower, and (2) In the presence of the same complications which may cause a microcytosis, namely, prolonged bleeding, chronic infection, endocrine disturbances or a dietary deficiency.

4 *Response to Treatment* The characteristic response to treatment may be considered under two headings (1) Clinical evidence of improvement and (2) Changes in the blood. They both appear promptly that is, usually between three and six days after therapy is begun. At this time every evidence becomes apparent that the patient's condition is changing for the better. This is indicated by the disappearance of nausea and vomiting, the appetite is greatly improved, if fever is present, the temperature falls to normal, the patient regains his strength rapidly and, in a relatively short time, is able to be up and about. There are very few conditions encountered in the practice of medicine which show such a remarkable and prompt response to specific therapy.

Indication of improvement in the blood is evidenced, first, by a striking increase in the number of reticulocytes, which begins between the third and sixth days after treatment, reaches the highest peak between the seventh to ninth days, and returns to normal at about the end of two weeks. With this change, the total erythrocyte count increases at about the rate of 200,000 to 400,000 red blood cells a week, depending upon the initial level of the erythrocyte count, the potency of the antipernicious anemia therapy, and the presence or absence of certain complications, such as infection. When these two characteristic responses occur it does not necessarily mean that the patient has pernicious anemia but it does indicate that either the disease is present or that the patient has a pernicious anemia-like blood condition which is seen in association with

certain disorders of the digestive tract, including liver disease, or the macrocytic anemia of pregnancy, *Dibothriocephalus latus* infestation, sprue and possibly pellagra

The absence of such a response is clear-cut and almost conclusive evidence against the diagnosis of pernicious anemia, provided the red blood cell count is below three million and a liver extract of known potency has been administered parenterally in appropriate doses. It is true that the hematological response may be less in patients who have an acute infection or extensive arteriosclerotic changes, but it is never, under any circumstances, completely lacking

5 *Paresthesia* One of the most constant subjective evidences of this disease is the presence of numbness and tingling of all four extremities. In most textbooks it is stated that this complaint is present in about 80 per cent of these patients, but if specific information is obtained concerning this symptom, it will be found to be present in 90 per cent of the cases. It is encountered in patients who have involvement of the nervous system due to other causes, but in these conditions it is not so common to have it involve both the hands and the feet, as it almost uniformly does in pernicious anemia. The absence of this symptom does not eliminate the disease as a diagnostic possibility but indicates that a careful search should be made for some other explanation of the patient's condition

6 *Glossitis* Careful questioning of patients with pernicious anemia will reveal that about two-thirds of them give a history of having had attacks of glossitis, characterized by periodic recurrences of painful, sore tongue. The patients usually state that the condition almost invariably has remissions and exacerbations. The term "recurrent glossitis" is, therefore, appropriate. In addition, 42 per cent of our group had definite and easily recognizable atrophy of the papillae of the dorsum of the tongue, about which there could be no doubt. It is interesting to note that a patient's tongue may appear perfectly normal despite a history of severe recurrent glossitis and, on the other hand, there may be obvious atrophic changes without a previous history of symptoms referable to the tongue. Another observation in our experience has been that never has a patient with pernicious anemia been observed with an abnormally coated tongue when an anemia is present, regardless of the intensity of the symptoms. In general, it may be said that the existence of a coated tongue in a patient suspected of having pernicious anemia, casts considerable doubt upon the diagnosis

Neither a history of glossitis nor atrophy of the tongue are conditions which are commonly encountered in clinical medicine and when present they should always suggest the possibility that the patient has pernicious anemia. It should be kept in mind, however, that similar tongue symptoms may occur in other conditions, such as sprue, pellagra, achlorhydric-microcytic anemia and various intestinal disorders.

7 *Leukopenia, or the Absence of Leukocytosis* A diminished number of leukocytes is almost always observed in patients with pernicious anemia who have an anemia and are in a condition of relapse. This is true even in the presence of a severe pyogenic infection which ordinarily would evoke a leukocytic response. There is a tendency for the leukocytes, however, to increase in number at the beginning of a remission, either spontaneous or therapeutically induced. Moreover, it is a well known fact that if an infection occurs at that time, there may be an exaggerated response as indicated by a striking rise in the leukocytes to a level of 30,000 or 40,000 or greater. A leukopenia then is the rule during relapse. A leukocytosis which has been reported during this stage may well be an erroneous observation, which can be accounted for by the enumeration of nucleated erythrocytes in the counting chamber as leukocytes.

#### SPLENOMEGALY

The older observers state that the spleen is palpable in perhaps 20 to 40 per cent of the cases. If this was the situation then, it is not true now, for it is rare to observe a spleen which is enlarged to a point where it is palpable beneath the left costal margin. Furthermore, the presence of a grossly enlarged spleen is strongly suggestive evidence that the patient has some cause other than pernicious anemia for the anemia. This is most frequently one of the lymphoblastoma group, such as aleukemic leukemia or Hodgkin's disease. Widespread liver disease, such as cirrhosis, may be associated with a macrocytic anemia and a moderately enlarged spleen. The anemia may be accounted for on the basis that there is inadequate storage of the erythrocyte maturing factor in the organ, and the splenic enlargement has been regarded as due to chronic congestion.

#### REMARKS ON THE TREATMENT OF PERNICIOUS ANEMIA

Twelve years have now passed since the modern treatment of pernicious anemia was introduced by Minot and Murphy. During that

interval, ample opportunity has been afforded numerous observers to study the effects of various types of treatment and compare their results with those noted before the existence of specific therapy. Prior to 1926, the status of the treatment of pernicious anemia is well expressed in the following quotation from a monograph on pernicious anemia published by Dr. Frank Evans, just a few months before the liver treatment was introduced. He states: "The treatment of pernicious anemia is discouraging. No patient with true pernicious anemia has ever been cured. However successful any therapeutic procedure may have been at first, there comes a time when the patient does not react to any treatment, he gradually grows worse, and death ensues. Furthermore, no treatment has so far been suggested which can be shown to have prolonged life."

The conclusions regarding treatment which are expressed in this article, are based upon the observation of approximately 1,000 patients who have been treated by various methods of liver and stomach therapy between the years 1927 and 1938. They have been observed, at intervals, for periods varying between a few months and eleven years.

Of this group, approximately 10 per cent, or 100 patients, are dead. The fatal cases can be divided into two main groups of equal importance numerically. First, those who died of complications incident to extensive involvement of the nervous system, and, second, those who died of incidental and unrelated diseases. The first group still remains a challenge to the methods of treatment of pernicious anemia and calls for an improvement especially in the management of the spinal cord lesions. The second has no direct association with pernicious anemia but is concerned with the prevention and treatment of unrelated diseases, chiefly degenerative, which are a common cause of death of persons who belong to the middle age or elderly group. None of the patients in either group as far as could be determined, died of anemia *per se*.

#### THE EFFECT OF TREATMENT ON SPINAL CORD LESIONS

Whereas one-half of the patients who died, did so as a result of complications incident to spinal cord changes, a very large proportion of these, either presented themselves for treatment for the first time when the neurological manifestations were advanced, or failed to follow instructions regarding treatment, and, as a result, the anemia failed to improve or there was a hematological relapse. Furthermore, many of them were treated before the more effective parenteral methods of administering

of the disease at present is the intramuscular administration of liver extract. This has the advantage of eliminating all question of absorption from the gastrointestinal tract, the blood can be maintained at a normal level by an injection given at intervals of one to three weeks, and this form of treatment will be successful in patients in whom the oral method fails.

There is a possible, but unproven, danger that in using the highly refined products, some substances may be eliminated which are beneficial to the patient. Crude liver extract is known to contain the entire vitamin B complex and it is considered that this substance is related to the pathologic changes in the spinal cord. There are, however, no data which indicate that the addition of vitamin B influences favorably either the blood or changes in the nervous system.

## THE NEUTROPENIC DISEASES\*

ROY R. KRACKE

THE estimation of the white blood cells has been done now for over fifty years but up until just a few years ago a decrease in the number of leukocytes was regarded only as a diagnostic sign. However, within the past fifteen years neutropenic states have assumed more and more importance not only because of the appearance of new diseases characterized by neutropenia but also because it has become generally recognized that when the white blood cells fall to a low level the patient occupies a precarious position because neutropenia means increased susceptibility to bacterial invasion. It is quite possible that the degree of susceptibility to infection may in some instances be inversely proportional to the number of circulating neutrophils. Furthermore, this lends renewed emphasis to the work of Metchnikoff, who nearly fifty years ago emphasized the predominant role of circulating blood cells in combating bacterial invasion. Since his time the pendulum of emphasis has swung toward the role of immune bodies rather than the cellular theory of body defense. If careful study of the neutropenic diseases serves to re-emphasize the importance of cellular body defense, it will indeed be worthwhile.

Up until recent years the various leukopenic states were usually called "secondary" because they were known to accompany some other disease process. We are quite familiar, of course, with the numerous diseases that are stated to be characterized by neutropenia. These include such common ones as measles, German measles, mumps, respiratory influenza, malaria in its chronic form, the recently recognized Brucellosis, typhus fever, early typhoid fever, and even overwhelming infectious processes produced by pyogenic organisms. Furthermore, a neutropenia is often seen in such conditions as Banti's disease, some of the lymphogranulomata, Hodgkin's disease occasionally, glandular tuberculosis, and in many conditions in which the bone marrow is directly involved, such as multiple myelomata, miliary tuberculosis and bone marrow carcinomatosis.

It is frequently stated in textbooks that such secondary neutropenic

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syndromes are brought about by the action of bacteria or their toxins. This seems to be an unsatisfactory explanation for I know of no scientific evidence that proves that certain bacterial toxins may depress leukopoietic function unless it be the work of Dennis,<sup>1</sup> who placed collodion capsules containing growing bacteria in the peritoneal cavities of rabbits and observed the leukocyte depression that followed the absorption of the bacterial toxins from the capsules. In some of the infectious diseases, no doubt, neutropenic disorders occur because the available circulating leukocytes are speedily drawn to the source of infection in an effort to combat it and this would explain this type of neutropenia more satisfactorily than to assume a toxic effect of bacterial toxins on marrow activity.

Many of the infectious diseases are characterized by severe types of neutropenia in occasional instances. I have observed a young university student who was admitted to the hospital with a leukocyte count of 800 with 10 per cent neutrophils and who was given a tentative diagnosis of agranulocytosis, yet who four days later developed the typical rash and clinical findings of typhus fever with a speedy return of the leukocytes to normal. Only recently I studied a young girl who for four days had suffered from profuse watery diarrhea with severe abdominal cramps and high fever and who on admission to the hospital showed a leukocyte count of 700 with 6 per cent neutrophils. A tentative diagnosis of agranulocytosis was made but bacterial examination of the stools revealed practically a total absence of the normal bacterial flora and practically a pure culture of *Bacillus paratyphosus* B was obtained. After recovery her leukocyte count returned to the normal level. Here was an instance then of food poisoning by this organism accompanied by an extremely severe neutropenia which lasted for several days. I should point out that this patient was particularly fortunate that during this time she suffered from no further bacterial invasion of the tissues. These examples illustrate the extremely low level to which the leukocytes may fall in response to certain types of infectious diseases. In such instances how can one explain the mechanism of leukopoietic depression? Is it because the bone marrow was overwhelmed by bacterial toxins or were the leukocytes drawn to the area of infection as fast as they were produced? I do not believe that the answer to this question can be stated at this time.

In addition to the infectious diseases that are accompanied by leukopenic disorders, there are other agents capable of producing this syndrome. Among these is benzene ( $C_6H_6$ ) which when injected into

laboratory animals practically invariably produces severe leukopenia within three to four days. Also if benzene is given to animals or to the human by mouth, chronic leukopenic disorders will usually result. It has not been many years since this product was used in therapeutics to reduce the white cell count in cases of chronic myelogenous leukemia. For many years in our laboratories at Emory University we have attempted to determine the mode of action of benzene on the leukopoietic centers and we are impressed with the concept that benzene does not reach the bone marrow as such but that it undergoes chemical transformation before action on the marrow, although I am unable to state its exact chemical state when it reaches the marrow cells. Benzene does not confine its action to the leukopoietic centers, particularly if given in large doses, but involves erythropoiesis and thrombopoiesis as well. Many animals poisoned with benzene show the hematologic picture of complete marrow aplasia just as does the human being who may develop aplastic anemia if unduly exposed to this agent. There are other chemical agents known to be capable of depressing the leukocyte count in an occasional individual. These include arsenic occasionally in its inorganic form and gold salts, some of which do not contain the benzene ring. Even gasoline fumes according to Alice Hamilton<sup>2</sup> may cause a depression of leukocytes and there are probably others closely related to benzene that have not yet been emphasized in medical literature.

The effect of excessive radiation on the bone marrow has long been known to be characterized by leukopenic disorders as was so well demonstrated by the famous instances of aplastic anemia following exposure to gamma rays in the incidence of poisoning among the luminous clock dial painters<sup>3</sup>. Also severe leukopenia has been reported from the drinking of so-called "radio-active water" and among a few individuals who have worked with radium. It has been reported in a sufficient number to clearly indicate that leukopenic disorders can arise from it. Even Roentgen rays have been reported in numerous instances to have produced severe leukopenic states.

I feel that I should point out again, as I have previously, that there seems to be some danger of the development of leukopenia in an occasional person who has been subjected to excessive radiation from sunlight. I have studied the blood of many people on their way to and from Florida where sunlight seems to be the chief object of the journey and I can not escape the impression that leukocyte counts are lower after

excessive exposure to the rays of the sun

It is well established now that a deficient diet may be responsible for leukopenia. This has been shown by Langston and Day<sup>4</sup> at the University of Arkansas, who have been able to produce consistently chronic leukopenia, erythropenia and thrombocytopenia in monkeys after feeding them with a diet deficient in vitamin G. Furthermore, Miller and Rhoads<sup>5</sup> have produced similar evidence that a black-tongue producing diet in dogs may be accompanied by leukopenia and stomatitis. Therefore, in the treatment of the neutropenic diseases it would be well to consider carefully the diet of the patient and to provide one that is not lacking in any of the essential vitamins.

It has been long recognized that marked leukopenic states may accompany disease involving the adrenal cortex and in particular it is a consistent finding in Addison's disease which is characterized by weakness, fatigue, marked hypotension, occasionally pigmentation of the skin, and nearly always severe leukopenia. As to whether or not this leukopenia is brought about by deficiency of the adrenal cortical hormone is open to question. Britton and Corey<sup>6</sup>, at the University of Virginia, have commented upon the marked leukopenia found in their adrenalectomized cats.

It would be well at this point to discuss another large group of agents that are now definitely recognized to be capable of producing the most severe neutropenic states. I refer to the various pain relieving drugs that have attracted so much attention in recent years. It has now been seven years since I first pointed out that certain pain relieving drugs may cause the disease, agranulocytosis. The first intimation to us that this could be possible was the admission of a patient to the Emory University Hospital in 1930. This patient was a middle-aged woman who had been ill with so-called influenza for several weeks and who during that time had been given a considerable number of analgesic agents, including amidopyrine, phenacetine and acetanilid. This patient was brought to the hospital because of her peculiar blue color which was soon determined to be due to methemoglobinemia. It was apparent, of course, that the methemoglobinemia in this instance was caused by prolonged administration of acetanilid. Much to our surprise we discovered also that this patient had agranulocytosis. The association of these two findings led us to our first realization that these drugs may be responsible for the leukocyte depression. I shall not burden you with a recital of the development and final proof of this concept but shall merely point out that a study of the cases

of agranulocytosis that we had seen up to that time, on careful questioning of the relatives of the deceased patients, added evidence to the effect that all of them had taken such drugs prior to their illness. These findings, coupled with statistical studies which showed that people who developed agranulocytosis were the largest drug users and that the geographic incidence of the disease corresponded to countries where those drugs were in wide use, added further support to the concept. For two years then we attempted to produce the disease in laboratory animals by the feeding and injection of such preparations as amidopyrine, pyramidon, acetanilid, phenacetine and proprietary mixtures of these, but were not able to do so. The final proof of the correctness of this concept has come from two lines of research. One of these, and the most conclusive, has been the occasional experimentation that has been carried out in which patients who have recovered from agranulocytosis have been given as little as a single dose of amidopyrine and the disease reproduced in them. This type of experiment has been carried out by Madison and Squier<sup>7</sup>, and subsequently by others throughout the world and has produced in my opinion ample confirmation that an occasional individual is so sensitive to the action of these drugs that the bone marrow may suddenly be thrown into a non-productive state by the ingestion of as little as a single therapeutic dose.

The second confirmation of this concept has come from Denmark where Plum<sup>8</sup>, in his most exhaustive monograph on this subject, has shown that up until 1934, there were over one hundred cases of agranulocytosis in that country and that the increasing incidence of the disease up to that time exactly paralleled the consumption of amidopyrine which in that country is imported, and that when the use of amidopyrine was forbidden by Government decree the disease at once completely disappeared. So today in Denmark, because of careful restriction in the use of this drug, the entire question of agranulocytosis has apparently been completely settled.

In addition to amidopyrine certain other drugs will produce marked leukopenic disorders. These include the organic arsenical compounds as well illustrated by the numerous instances of agranulocytosis and aplastic anemia that have followed the injection of as little as one dose. It has long been recognized that arsphenamine in an occasional person may produce aplastic anemia and I believe that it should be emphasized that this type of drug can also produce a hematological syndrome that is actually

agranulocytosis in which the marrow depression is limited exclusively to depression of the granulocytes This is well illustrated by the recent report of Blew,<sup>9</sup> from the United States Navy, who observed agranulocytosis in three young sailors, one of whom had received sixty-eight injections of neoarsphenamine, another having received a large number and a third having received only three injections In these patients the red cell pictures were not affected Such observations, coupled with many others in the literature, indicate very clearly that the organic arsenicals can produce agranulocytosis as well as aplastic anemia Furthermore, I have observed a colored boy who developed this disease after one injection of neoarsphenamine It is well established now that the administration of dinitrophenol can produce marked leukopenia since several instances have been reported Since dinitrophenol, however, produces cataracts in an occasional person as well as agranulocytosis, it is today no longer a serious problem in this respect I do not believe that well informed doctors use dinitrophenol any longer

The drug causation of neutropenic diseases has received and should receive renewed emphasis at this time since the introduction of sulfanilamide I am able to find records now of fourteen instances of agranulocytosis following the administration of sulfanilamide In these fourteen, which have been reported from widely scattered areas, in every instance the dosage of the drug has been quite large and in most of them has extended over a period of several days to several weeks I am unable to find a record of the disease having followed small quantities of this preparation, such, for example, as one or two doses, and in this respect this type of leukopoietic depression seems to differ from that produced by amidopyrine Furthermore, it should be pointed out that sulfanilamide in an occasional patient produces neutropenia of a mild to moderate degree and not to the point of complete agranulocytosis I had observed patients with leukocyte counts around two, three or four thousand cells, the reduction in the cells being at the expense of the neutrophils Such patients usually recover from the depressing effect of the drug unless the count has fallen so low that they have become invaded by pathogenic bacteria in which event, of course, death may be brought about by the overwhelming sepsis just as in other cases of agranulocytosis I have been particularly concerned recently in the effect of sulfanilamide on the blood and have observed now several instances in which this preparation is capable of producing a marked stimulation of the leukopoietic centers

resulting, therefore, in extremely high leukocyte counts and I note that this observation is recorded fairly frequently in the medical literature. I have observed leukocyte counts over one hundred thousand per c mm during the course of treatment with sulfanilamide and it is not unusual to see leukocyte counts of thirty, forty or fifty thousand cells per c mm of blood. I am unable to explain why sulfanilamide in an occasional person will depress leukopoiesis and in another person apparently stimulate leukopoiesis. Of course, this drug is also capable of producing in an occasional person marked degrees of hemolytic anemia and in these instances, a high degree of leukopoietic activity usually accompanies the regeneration of red cells. The fact that sulfanilamide itself produces leukocytosis in an occasional person, often has an important practical bearing on the treatment of the patient in question. For example, I have observed a young woman who developed streptococcic puerperal sepsis and was treated intensively with sulfanilamide for six days. At that time her leukocyte count was sixty thousand per c mm and at the same time she had shown such marked improvement that it appeared clinically that the infection had been overcome. The question that presented itself then was—What was the cause of the leukocytosis? If it were caused by sulfanilamide then there was no cause for alarm but, on the other hand, if it meant that the infectious process was still rampant, then further therapy with sulfanilamide was clearly indicated. I have observed this same problem now in several such instances and it presents the question as to when the drug should be discontinued.

Finally, in concluding this discussion of drugs, it must be pointed out that amidopyrine has been combined with so many other preparations and the resulting compounds sold under such a wide variety of names, that it is practically impossible for the physician to know whether or not the average pain-relieving preparation contains the drug. In recent publications I have shown a large number of preparations that contain this particular drug, so I will not repeat it here. The fact that amidopyrine has been so widely used is a testimonial to its therapeutic efficacy in the relief of pain and, of course, it is widely recognized as a valuable agent for that purpose. However, if the physician chooses to use amidopyrine, he should do so knowingly and should write a prescription for it. In view of the dangers of this drug, I can see little excuse for physicians prescribing various compounds manufactured by different drug firms which may or may not indicate the presence of the drug. I am well aware of the fact

that the desk of the average physician is daily cluttered up with literature and samples from various drug firms extolling the virtues of their various preparations, so much so that the average doctor nowadays is lost in a maze of commercial pharmacology. It appears to me that the science of pharmacology among doctors is a lost art. If one chooses to use amidopyrine and other similar compounds it should be done by prescription and we should not depend for pharmacological knowledge on the literature of drug manufacturers or upon the exhortations of detail men. The new food and drug law which will become effective shortly offers some measure of protection to the public against the consumption of such preparations unknowingly since it requires the formula of patented compounds to be printed on the package. It will be possible, therefore, for that part of the public that is informed on this question to read the label and see whether or not a patented compound contains dangerous drugs.

Since it is now obvious that leukopenic disorders can be caused by such a wide variety of physical agents, chemical compounds, drugs, dietary deficiencies and hormone disorders, it is incumbent upon the physician when confronted with a patient with leukopenia to make careful search for possible causative factors, in order that the cause may be removed. This may prove to be the most important part of the treatment.

I shall now discuss briefly those diseases of the blood that are characterized by neutropenia. According to modern classifications these are three in number as follows: agranulocytosis, aplastic anemia, and aleukemic leukemia. In view of the previous discussion of the factors that are capable of depressing the leukocytes of the blood, it is unnecessary to consider further the etiology of agranulocytosis except to state that the evidence seems quite adequate that the great majority of these cases are caused by the ingestion of some of the drugs mentioned before and notably amidopyrine.

I am quite ready to admit, however, that all cases of agranulocytosis are not caused by ingestion of drugs. There is some evidence to indicate that the disease may arise from an infectious origin, or for that matter from a filterable virus. In this connection there is a recent report of considerable interest from Lawrence and Syverton<sup>10</sup>. These workers discovered an instance of spontaneous agranulocytosis in a cat and were able apparently to transmit the disease through ten series of cats by the injection of the agranulocytic livers of the preceding animals. They concluded

that there is in the cat a transmissible disease which seems to be caused by a filterable virus which is characterized by severe neutropenia

Within the past three years there has been apparently a reduction in the number of cases of agranulocytosis but with the increasing use of sulfanilamide I am of the opinion that a new wave of the disease may make its appearance

The chief diagnostic finding in agranulocytosis is the extreme leukopenia. The cellular reduction, however, is not confined to the neutrophils but involves the other blood cells as well. Therefore, a more correct designation of the condition would probably be, malignant leukopenia. The method by which the offending agent depresses the marrow function is not known. It is probable that the marrow depression antedates the leukocytic depression in the peripheral blood. I have had opportunity to study one patient with daily blood studies before the leukocyte depression became obvious in the blood stream and also of studying the same patient for four days before clinical evidence of the disease became apparent. It seems that the condition develops first by a cessation of cellular output from the marrow, this in turn causing a slow decrease of the leukocytes of the blood and then the neutrophils may be entirely absent for several days before clinical symptoms appear. The clinical symptoms in most instances result from bacterial invasion. Therefore, when the patient is first seen the disease is usually in what may be termed "the terminal stage of the process". Most patients when first seen have already become the victims of varying types of bacterial invasion and may present varying degrees of ulceration of the soft tissues of the oral cavity or about the anus or vagina and in some instances blood stream invasion may have already taken place. There has been some question concerning the pathology in the bone marrow and in former years it was believed that the marrow becomes aplastic in its cellular content with an actual quantitative decrease in the leukopoietic centers. However, Fitz-Hugh and Krumbhaar<sup>11</sup> have pointed out that in many cases the marrow was actually hyperplastic and in my experience this has proved to be true. There seems to be an arrest of development of the neutrophils in the marrow, this usually taking place at the myeloblastic level so that actually the marrow may be crowded with young, immature leukoblasts and in this respect the pathology of the marrow does not differ from that often times seen in the marrow of a patient with aleukemic leukemia. Furthermore, as Rhoads has demonstrated, even in aplastic anemia in

which the peripheral blood has become markedly depleted of all cell types, the marrow in those patients may also show such a hyperplasia. This gives rise to the possibility that common etiological factors may be operative in some of these diseases, producing varying types of hematologic pictures in the peripheral blood, and a variety of clinical syndromes.

The patient with agranulocytosis seldom shows any disturbance of the red cells and hemoglobin unless the process should happen to become prolonged. Furthermore, the platelets in the blood are usually not disturbed. I should like to point out, however, that there is no reason why a patient with agranulocytosis should not be anemic and indeed many of them are anemic because a considerable proportion of them have been suffering with other diseases beforehand.

In my opinion the presence of clinical hemorrhage does not rule out agranulocytosis. I have studied typical instances of this disease which at autopsy showed varying degrees of hemorrhage, usually in the form of petechial spots. This, however, is not the usual finding. The patient with this disease obviously will present a variety of clinical symptoms, depending not only upon the extent of reduction of the white cells but also upon the degree of bacterial invasion. Ulcers of the soft tissues in areas normally inhabited by bacteria are common. There is usually a definite febrile course and in many patients there is marked edema of the soft tissues about the mouth and the neck. This predominant edema which occurs so often seems to be an attempt at a cellular response to invasion of organisms, but since cells are not available for this, the inflammatory response is mainly one of fluid into the tissues.

In many instances patients with agranulocytosis exhibit a degree of prostration which seems entirely out of proportion to the physical findings. I have studied patients who showed a completely negative physical examination and in whom no external lesions of any sort could be found, yet the same patients presented a high fever, were partially comatose, were sometimes irrational and delirious. Even at autopsy it was extremely difficult to find gross pathologic changes that could account for such severe clinical manifestations.

The treatment of agranulocytosis still remains highly unsatisfactory in spite of the many efforts made and new preparations introduced to combat it. It would require a long recitation for me to enumerate the therapeutic agents that have been used in this disease, suffice it to say that these have now centered around the use of repeated blood trans-

fusions, liver extract by injection in large amounts, pentnucleotide or other nucleic acid products by injection, and yellow bone marrow given by mouth. There seems to be little benefit from the use of radiation. I am convinced that if there should be a choice between agents used to stimulate a renewed marrow output, liver extract would be much preferable to pentnucleotide. Our experience with pentnucleotide has been quite disappointing, but here I should point out that no one man probably has treated a sufficient number of cases to form a proper evaluation of therapeutic agents. After all, in this disease do we not expect too much of any therapeutic agent, especially in view of the considerations that I have brought out before, that is, not only is the patient depleted of granulocytes, but in addition to this, often times has become overwhelmed with invading organisms, so that there are two serious and distinct diseases to treat, either of which promises to be fatal. It is indeed expecting the impossible of a therapeutic agent that it be able not only to stimulate renewed output of leukocytes but also to successfully combat overwhelming infection.

Although the use of yellow bone marrow by mouth has been recommended, I do not believe that adequate evidence as yet has been presented to prove its therapeutic efficacy. Agranulocytosis, however, is an emergency illness and the use of any therapeutic agent is justifiable if it offers any promise whatever. Therefore, it is my practice to recommend the use of all of these things I have just enumerated, that is, blood transfusions repeatedly, liver extract in ten times the ordinary dosage by injection, pentnucleotide, yellow bone marrow by mouth and symptomatic therapy, but even with all of these, the mortality rate in our more recent series of cases very closely approximates that of the earlier years.

In this paper I shall not attempt to discuss aplastic anemia since this question has been adequately presented by Dr. Rhoads, except to point out that I know of no therapeutic agent that has proved to be of any success in the treatment of this disease, particularly the so-called "idiopathic" type. I have observed patients with hematological aplastic anemia following arsphenamine therapy who usually recovered with cessation of the injections of the drug and the use of transfusions.

The other disease of the blood characterized in many instances by severe leukopenia is that known as aleukemic leukemia. This disease is unquestionably a part of the general leukemic process. It is characterized by hematological findings that in some instances are extremely difficult

to evaluate. The patient usually shows a reduction in the number of red cells depending upon the severity and duration of the process, and in my experience the red cell picture is usually a macrocytic type of anemia. The patient also may present varying hemorrhagic disorders because of a reduction in the number of blood platelets. If they are below fifty or sixty thousand per c mm, hemorrhages may supervene at any time.

A characteristic feature in nearly all of these cases is a moderate to severe reduction in the total number of leukocytes. The cells may range from the normal figure, or slightly above, down to only a few hundred cells per c mm and the lower the cell count, the more precarious becomes the status of the patient. Furthermore, the same patient may show a great variation in the number of leukocytes at different times. I have observed a child with a leukocyte count of four hundred cells per c mm and nearly all of these cells were myeloblasts. Six days later this same patient had a total leukocyte count of one hundred and sixty thousand per c mm with death shortly afterwards. This merely illustrates the extreme variations in the total number of leukocytes that may be seen in what appears to be aleukemic leukemia. However, many of the more chronic forms may extend for months and perhaps years with an extremely low leukocyte count, only two, three or four thousand, with the percentage of granulocytes quite low. Finally such patients may die because of intervening infectious processes or the count may suddenly become elevated so that what was formerly a chronic type of aleukemic leukemia suddenly changes to an acute form usually of the myeloblastic type with an early termination.

Naegeli stated that the patient with aleukemic leukemia usually lives longer than those patients with high cell counts. Assuming that both are chronic in type, this has not been my experience. The chronic form of aleukemic leukemia does not have, in my experience, the life expectancy of the patient with chronic myelogenous leukemia with high cell counts.

The physical findings in these patients are quite variable, some may show splenomegaly and others not show this finding. Many of them have complications of hemorrhagic disorders, most of them show variable degrees of anemia, some show intercurrent episodes of infection. The treatment seems entirely unsatisfactory. A multitude of therapeutic agents have been employed. Blood transfusions, of course, remain the bulwark continually to restore depleted red cells and perhaps leukocytes. All types of hematologic agents have been employed with no success. Radiation is

usually employed, sometimes directed toward the spleen, if there is splenomegaly, and occasionally as a spray over the bony structure I do not believe that there is evidence to indicate that these patients are materially benefited even by radiation. Whether or not their life is prolonged by its use, I am unable to state. I do know that we lose these patients invariably after varying periods of time.

Finally I would like to mention a rather obscure leukopenic syndrome that has repeatedly come to my attention, one I have termed "chronic neutropenia", which may have its origin from any of the causes I have enumerated before. This is occasionally seen in the half-well and half-sick patient who often times haunts the doctor's office. Such a patient may show a leukocyte count of only two to three thousand, this being at the expense of the neutrophils. They seem unusually susceptible to excessive fatigue, easy tiring and increased susceptibility to infection. Such patients may present this syndrome over a long period of time and in some of them the use of liver extract by injection has proved to be a valuable agent, whereas in others the correction of dietary deficiencies seems to be the proper treatment.

In conclusion, I desire to emphasize the multiplicity of factors that apparently are conducive to the neutropenic state and the necessity for careful investigation relative to these factors in every patient who presents this syndrome. Especially is this important in view of the inadequacy of our present therapeutic agents. I believe that we can do much more for the neutropenic syndromes by working toward their prevention than by correction after they have once developed.

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RECENT ADVANCES IN KNOWLEDGE OF SOME  
OF THE COMMON DISEASES OF CHILDHOOD\*

S Z LEVINE

RECENT advances in medical knowledge have modified the diagnosis and treatment of so many of the common diseases of childhood that to cover the subject fully would entail a systematic review of practically the entire field of pediatrics. In the space allotted, a presentation of this nature would, necessarily, deteriorate into a cursory and superficial resumé of recent medical publications with no attempt at critical appraisal. In this article I propose rather to follow a more selective course.

A number of fundamental investigations have been reported in recent years which promise to be of outstanding significance in the future development of medical progress. Amongst these must be included the work of Stanley on the essential nature of filterable viruses, the biochemical investigations of Urey on heavy isotopes and their use in the elucidation of physiologic problems by Schoenheimer and his co-workers, the identification of the chemical structure of various vitamins and hormones by a number of workers and, in the use of sulfanilamide, the renewed demonstration by Domagk of the value of chemotherapy. The objectives dictating the choice of subjects discussed here will however be those of present practicability and usefulness.

In recent years the pediatrician has been presented with numerous methods of diagnosis, prophylaxis and treatment. Before accepting a new procedure for general use, the results of clinical trial under controlled conditions should be critically examined. Discrimination is needed to avoid either excess haste or needless delay in utilizing experimental results in general practice. I shall undertake the admittedly hazardous task of attempting to evaluate the present state of our knowledge regarding some of these newer procedures, realizing full well that such a plan of presentation leaves one open to justifiable criticism since the choice of subjects may be considered inept and the assessments of

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value erroneous. Because of limitations of space, detailed evidence supporting evaluations will be omitted and I hope statements which may seem dogmatic will be condoned.

### INFECTIONS OF THE URINARY TRACT

The high incidence of infections of the urinary tract in childhood, their potentially serious consequences and the changing concepts of diagnosis and treatment make consideration of pyuria advisable. By the term pyuria is meant the persistent presence of clumps of pus and bacteria in uncentrifuged, "clean" or catheterized specimens of urine and not an occasional white blood cell in a casual specimen. Until recently pyuria as a complication of upper respiratory infections in children aroused little apprehension since the attending pediatrician was aware that the condition was as a rule self-limited, clearing after a shorter or longer period on a regimen of forced fluids and the administration of alkalis or drugs such as methenamine and acid phosphate. A series of recent discoveries have continuously modified the treatment of this acute condition.

Following the demonstration by Helmholtz that high fat, low carbohydrate diets accelerated recovery by leading to the excretion of an acid urine with a high concentration of beta-hydroxybutyric acid which was bactericidal, this form of therapy was frequently used. It never became popular however because of the difficulty of persuading children to take these unpalatable diets.

Shortly thereafter Rosenheim found that the results obtained with the ketogenic diet could be duplicated more easily by the administration of mandelic acid. This aromatic acid is neither conjugated nor oxidized in the body but is excreted unchanged, imparting a high degree of acidity to the urine. To facilitate this, the ammonium salt—which is less irritating than the free acid—is administered and if the desired acidity is not secured by the use of ammonium mandelate alone, ammonium chloride or acid sodium phosphate may be used.

The following technique for mandelic acid therapy is recommended. Elixir of ammonium mandelate (a 25 per cent solution) is given by mouth in dosages of from 1 to 3 drams four times daily, after meals. This dosage supplies from 4 to 12 grams of mandelic acid daily. Infants under one year receive 4 grams daily, children over ten years, 12 grams, and children of intermediate ages, intermediate amounts. This level of

dosage yields mandelic acid concentrations of 0.5 per cent or higher in the urine. Therapy is continued for a period of two weeks even though pyuria disappears earlier. During this time, the children are placed on an acid-ash diet and the fluid intake is adjusted to meet the fluid requirements. Urine specimens are examined at least once daily for sediment and acidity. Optimal acidity is represented by a pH of less than 5.5 as determined by the indicator, chlorphenol red, which turns from a pink to a yellow color at this reaction. If the desired acidity is not obtained after a day or two by the use of the salt alone, solution of ammonium chloride in daily dosages of from 2 to 8 cc. is added to the regimen. If bacteriuria or pyuria persists despite the two weeks of therapy, a rest period of one week is followed by a second course. If no results are obtained, continuance of this form of treatment is usually of little or no value.

At this point, a word of caution should be sounded. Mandelic acid therapy should not be employed in the presence of impaired renal function, large numbers of red blood cells in the urine or fever. When the pyuria results from infection by urea-splitting organisms such as *B. pyocyaneus*, *aerobacter* and *proteus*, the ammonium salts of mandelate or the accessory acidifier should be replaced by sodium salts.

Mandelic acid therapy has demonstrated its value in acute pyurias unassociated with congenital anomalies of the urinary tract where the offending organisms have been the common gram negative bacilli such as *B. coli* or the less common cocci, particularly *S. fecalis*.

The advent and increasing popularity of sulfanilamide led inevitably to its use in the treatment of pyuria in children and it has proved a potent therapeutic agent in practically all forms of acute urinary tract infections. The advantage of this drug over mandelic acid is that it exerts a sterilizing action in urine, either alkaline or acid. Fluid restriction, an acid-ash diet and accessory acidifiers are therefore unnecessary when sulfanilamide is employed.

The technique of this form of therapy as used in the children's clinic of the New York Hospital follows:

Sulfanilamide tablets are administered orally in a total daily dosage of 0.2 grams per kilogram of body weight, divided into four equal parts and given at six hour intervals. This dosage exceeds that recommended by Helmholz but we have found the larger amounts more effective clinically and only with the larger dosage have blood concentrations of

sulfanilamide been obtained within the accepted optimal range of 10 mg or more per 100 cc of blood

This therapy is continued for two weeks followed by a rest period of one week. A second course is instituted when necessary. Sulfanilamide should not be used in dehydrated or debilitated states, in the presence of severe anemia, leukopenia or nephritis. Therapy should be discontinued with the appearance of severe cyanosis, jaundice, sulphemoglobinemia or methemoglobinemia, hyperpyrexia, anemia or granulocytopenia. Morbilliform eruptions occur not infrequently but are of lesser import. With cessation of therapy and the forcing of fluids the above manifestations almost invariably subside. Saline purgatives should be avoided during therapy.

The conclusions expressed regarding the status of mandelic acid therapy also apply to sulfanilamide therapy. In the absence of congenital anomalies of the urinary tract or when the offending organism is not *S. fecalis*—a normal inhabitant of the intestinal tract—the pyuria and bacteriuria clear up in the majority of instances during the first two weeks of treatment.

Despite the proved efficacy of these newer forms of therapy, the pediatrician not infrequently encounters infants and children in whom the pyuria is resistant to all forms of medical treatment or may recur after temporary subsidence. In these patients irreparable harm may result from improper treatment. In our experience as well as in the far greater experience of Meredith Campbell and others, the persistent pyuria in a vast majority of these young patients is associated with a congenital anomaly of the urinary tract with consequent urinary stasis and secondary infection. Since many of these anomalies are amenable to surgical intervention a complete urologic study is obviously desirable, including intravenous urography, cystoscopy and retrograde pyelography where indicated. Disastrous crippling of renal function and atrophy of kidney parenchyma due to neglect of this condition are still all too common. There is no justification for following a so-called conservative course in a young child whose pyuria has resisted adequate medical treatment for longer than four, or at most six, weeks. Such youngsters should have the benefit of urologic consultation.

#### PERTUSSIS

None of the newer prophylactic measures has attracted more atten-

tion than the vaccines against whooping cough. The importance of this disease as a cause of death in infants is good reason for this attention. The yearly case rate in the United States is approximately 300,000 with 5,000 deaths, and the mortality rate of infants under two years is about 15 per cent of those affected. The difficulty of early diagnosis, and therefore of isolation during the highly contagious catarrhal stage of the disease, makes it probable that eventual eradication of pertussis will depend on the widespread use of preventive immunization.

Since the re-introduction by Sauer in 1926 of the use of vaccines for protection against whooping cough, the method has been widely publicized. Sauer's special contributions are the method of preparation of the vaccine and the higher dosage recommended. Hemolytic strains from freshly isolated cultures are grown on a solid medium containing human blood and the culture is carefully harvested with a minimum of washing in the preparation of the vaccine. The dosage advocated is 10, 15 and 15 cc injected intramuscularly in each buttock at weekly intervals, making a total of 8 cc or 80 billion killed organisms, given preferably between the ages of seven to ten months. In children over three years the latter two doses may be increased to 2 cc so that the total dose is 10 cc. Development of immunity, according to Sauer, requires from three to four months and its duration supposedly extends for from one to five years, according to different observers.

A number of other vaccines have been proposed for active immunization. These include the "undenatured" bacterial antigen of Krueger in which the organisms are killed by mechanical disruption rather than by chemical agents, the vaccine of Mishulow of the Department of Health of New York City in which the antigen consists of both organisms and toxic filtrate, mixed vaccines containing not only Bordet-Gengou bacilli but also streptococci and staphylococci, and finally a bacteria free filtrate detoxified with formalin. Most of the latter products are advocated for immunization in patients already exposed and the dosage recommended varies from 0.5 to 2 cc every day or every other day for two to six injections.

Conclusions regarding the efficacy of present day vaccines are still equivocal. Available statistical evidence is predominantly favorable, but the results which may be obtained in any given case are not predictable. Failures to immunize undoubtedly occur in many instances and many questions remain unanswered. If immunity develops, how long does

it last and how variable is it? What role does the frequently poor immunologic response of infants to injections of antigen play in explaining the failures which occur in this age period? Is the dosage at present in use optimal? It is known that humoral phenomena such as agglutinin response and complement fixation which result from injections with any vaccine afford criteria for tissue immunity which are not necessarily reliable

In our present state of knowledge, the conservative attitude toward these measures may be summarized as follows. The vaccines at present available merit continuation of experimental studies under controlled conditions but cannot as yet be recommended as a general public measure analogous to the accepted use of specific prophylaxis against smallpox and diphtheria. Since there is little indication that injections of pertussis vaccine are harmful, their use in younger children of large families, nurseries, and institutions where intimate exposure cannot be avoided and in older debilitated or tuberculous children may be countenanced since it offers hope of at least partial protection.

It is my belief that convalescent human serum injected in dosages of 10 to 20 cc intramuscularly in infants and older sick children during the incubation period of pertussis may reduce the severity of ensuing symptoms. A considerably higher number of observations are however necessary to validate this opinion.

### POLIOMYELITIS

Another infectious disease of considerable public concern is anterior poliomyelitis. Recent advances in knowledge of virus diseases in general and of this disease in particular have not as yet led to the discovery of successful prophylactic measures.

Early reports of successful protection against poliomyelitis by subcutaneous injections of either attenuated or inactivated virus have in the main not been substantiated. That these methods are not free from danger is shown by reports of the development of the disease in a number of children who were inoculated six to fourteen days prior to the onset of symptoms. Both Rivers and Flexner believe that in the present state of our knowledge, attempts to induce active immunization against poliomyelitis by injections of virus are unsound. "No methods have as yet been devised which can so modify the virus that it will retain its immunizing power or is merely reduced in potency so that it immunizes

in some instances and paralyzes in others”

Approximately 150 inoculations with an “inactivated” virus were given in our clinic in 1936 without the development of poliomyelitis in any of our cases, but in view of the evidence cited this procedure should be discouraged. Within the last month, Stanley and his co-workers have demonstrated that x-radiation of certain viruses results in destruction of their pathogenicity with retention of their antigenicity. This offers much promise for the future.

Because of the unsuccessful attempts to immunize actively against poliomyelitis by injections of virus, Armstrong and Harris used intranasal sprays of picric acid, zinc sulphate and other chemicals and protected monkeys against infection by the intranasal route. Although the animal work is fairly conclusive, it has not been confirmed for humans in its first field trial. During the recent epidemic in Toronto, reported by Brown, Tisdall and others, 4713 children were sprayed nasally with 1 cc. of a mixture of zinc sulphate (1 per cent), pantocain (1 per cent) and sodium chloride (0.5 per cent) on two occasions at ten to twelve day intervals. Twenty-five per cent of the children developed anosmia, indicating that the spray in this group had reached the olfactory nerve endings. Eleven subsequently developed poliomyelitis compared with an identical case rate of eighteen in 6300 control children.

Convalescent human serum as a means of passive prophylaxis and treatment has not been encouraging. The presence of humoral antiviral substances does not parallel tissue immunity, for monkeys have contracted the experimental disease even though their serum had neutralizing antibodies at the time of intracerebral inoculation of the virus.

To date, none of the recommended prophylactic procedures against poliomyelitis has demonstrated the combination of practicability, safety and effectiveness necessary for adoption as a public health measure, but the intensive studies currently being carried out presage valuable contributions in the near future.

## VITAMINS

Outstanding advances have recently been made in our knowledge of the biochemistry, physiology and clinical use of vitamins. A number of accessory food factors necessary for proper nutrition in infancy and in childhood have been obtained in pure form and their chemical structure identified. In many instances they have been synthesized and made

available for therapeutics. Earlier recognition of subclinical deficiency states may soon be possible for a number of vitamins because the physiologic functions subserved by these vitamins are being more accurately defined and simple chemical tests for assaying body reserves are being developed. Standardization of vitamins in terms of international or chemical units is replacing the tedious and uncertain technique of biologic assay in animals. The present discussion will be limited to clinical aspects of the subject.

*Vitamin A* Identification of the visual purple of the retina as a chemical sterol closely resembling vitamin A in chemical structure underlies the introduction of the biophotometer for detecting night blindness, a manifestation of vitamin A deficiency. Evidence collected throughout the country suggests that a surprisingly large number of both children and adults ingest inadequate amounts of this vitamin.

Wolbach has shown that lack of vitamin A is associated with widespread cornification and keratinization of mucosal epithelium in both animals and man and predisposes to infections. Because of this, there has been a growing tendency fostered by commercial concerns to assume that the resistance of children to infection may be augmented by increasing their intake of vitamin A. There is no evidence as yet that augmentation above accepted adequate levels of intake necessarily promotes the health and well-being of children. In our present state of knowledge, daily intakes of from 4,000 to 6,000 international units of vitamin A either in the diet, in the form of the provitamin, carotene, or as fish liver oil are presumably adequate to cover the needs of the growing child. In the presence of gastrointestinal disorders or chronic infections, larger intakes may be desirable.

*Vitamin B* The vitamin B complex has been divided into at least six component fractions and the chemical structures of three have already been identified. B<sub>1</sub> as thiamin, B<sub>2</sub> as ribo or lactoflavin, and the P (pellagra-preventing factor) as nicotinic acid. It is too early to delimit the precise role of each of these components in human health and nutrition. Reliable biochemical methods are not yet available for assaying the body reserves of any of the constituents of the B complex, criteria of early obvious deficiency states are still largely guesswork, and accurate information regarding levels of optimal intake is still lacking. The use by pediatricians of the vitamin B complex in a variety of ailments is easily understandable but more extensive, carefully controlled clinical studies

are necessary to prove the value of these therapeutic agents in human beings. Present knowledge indicates that a diet containing from 300 to 400 international units of vitamin B<sub>1</sub> and 600 Sherman units of B<sub>2</sub> adequately cover the requirements of growing children. Authentic data are not yet available regarding the other components of the vitamin B complex.

*Vitamin C* The identification of vitamin C as cevitamic acid (a glycuronic acid), its storage in the adrenal cortex and other tissues, the use of colorimetric tests of the blood and urine for estimating the body reserves are well established. That subclinical deficiency states occur, without the definite manifestations of scurvy, has been demonstrated by the use of tolerance tests in which the cevitamic acid content of the urine is determined following the ingestion of a test dose of the vitamin. Although deficiency of this vitamin has been implicated in a variety of diseases including acute rheumatic fever, poliomyelitis, diphtheria, upper respiratory infections, pertussis and symptomatic purpura, the causal relationship of lack of vitamin C has been generally accepted only in scurvy and dental caries. It should be mentioned that two other factors, designated "K" and "P", have recently been isolated from citrus fruits. These factors are apparently concerned with the coagulation of blood and with capillary permeability and appear to be separate and distinct from cevitamic acid itself.

The best available evidence indicates that the daily ingestion of from 150 to 300 international units or 10 to 20 mg. of crystalline cevitamic acid, equivalent in vitamin content to from 30 to 45 cc. of fresh orange juice, usually suffices to prevent the development of latent scurvy in infants and children. Amounts as great as 300 to 500 mg. of crystalline vitamin C have been administered orally and intravenously in the treatment of manifest scurvy without harmful effects.

*Vitamin D* Recent investigations of the fat soluble, anti-rachitic vitamin D have advanced our methods for insuring its universal consumption by growing infants and children. During the past decade Windhaus and Alfred Hess discovered the identity of vitamin D and irradiated ergosterol and Hess and Steenbock demonstrated that ultra-violet irradiation rendered a large variety of foodstuffs antirachitogenic. As a result commercial concerns raced to irradiate all of their saleable products—milk, cereals, peanut butter, bread, cocoa malt, cigarettes and even underwear, in this "era of irradiation."

following the course of treatment prescribed above first, patients in whom enlargement of the genitalia was produced without testicular descent, and second, cases, far fewer in number, in whom neither descent of the testes nor enlargement of the genitalia followed hormone therapy. In the first group it seems reasonable to assume that the penile enlargement indicates that at least one testis is present and capable of responding to adequate pituitary stimulation and that testicular descent is prevented by mechanical obstruction. These patients require operative intervention accompanied preferably by a course of hormone therapy before and possibly after operation. In the second group, complete failure following adequate dosage of gonadotropic hormone suggests either absence or atrophy of both testes, and that surgical treatment is also likely to fail. Such patients should be given androsterone or male sex hormone, although accurate knowledge concerning the ultimate results of such therapy will be obtained only with time.

#### VAGINITIS

The popularity of hormone therapy for gonorrheal vulvovaginitis is ample evidence of the generally unsatisfactory results obtained with other forms of treatment. According to the annual report for 1937 of a committee of the Social Hygiene Association, twenty of twenty-four special vaginitis clinics in New York City used estrogenic substance either exclusively or as an adjuvant to other forms of therapy. Treatment with the follicular hormone of the ovary, either from pregnancy urine or ovarian extracts, was introduced by Lewis for infantile vaginitis on the assumption that cornification of the vaginal mucosa by estrogenic hormone would render it less susceptible to the gonococcus. This supposition was confirmed by the successful results obtained in the first small series of infants so treated.

Since then, many observers have demonstrated its general, although not universal efficacy. The present aim of hormone therapy is to administer a dosage adequate to produce cytological changes in the vaginal mucosa and a lowering of the vaginal pH to 5.5 or less—changes which were not obtained constantly with the earlier smaller dosage used. It may be stated definitely however that such changes are not invariably accompanied by cure of the gonorrheal infection.

More than 150 infants and children have been treated with hormone by Dr. Dooley in the vaginitis clinic of the New York Hospital. The

present method is as follows Daily subcutaneous injections of from 2000 to as much as 10,000 I U of follicular hormone (in oil) are administered in increasing dosage until the desired change in cytology and acidity is obtained The findings are checked weekly and often more frequently by vaginal smears and nitrazene paper tests for pH The desired changes are usually obtained in from one to four weeks and sometimes earlier Although the vaginal discharge and the number of gonococci tend to be reduced by this treatment, complete cure in twenty or thirty days, as frequently reported, has been the exception rather than the rule in our experience

These less favorable results may be explained by the more stringent criteria for cure No child is considered cured unless all vaginal discharge has ceased, vaginoscopic examination shows a normal cervix, and three negative cultures as well as smears have been obtained

The complement fixation test is also used as a diagnostic and prognostic aid A high titre in the blood indicates, in our opinion, a gonorrheal etiology of the discharge even though no organisms are present in the smear, and maintenance of the high titre affords evidence that the infection persists and that symptoms may recur

The recent experience of Lewis suggests that local application of this hormone by daily vaginal instillation or suppositories is probably more effective than parenteral administration In a relatively small number of patients in our clinic, the use of daily vaginal estrogenic suppositories or capsules in dosages of 1000 I U has seemed to accelerate recovery, but far greater experience with this modification is necessary under the same carefully controlled conditions before universal acceptance No harmful by-effects such as hypertrophy of the breasts or precocious menstruation have been observed in our patients

The apparently favorable reports with sulfanilamide in gonorrheal infections offer promising implications for the treatment of vulvovaginitis but an adequate number of observations on its value in the latter are not yet available

Estrogenic therapy of gonorrheal vulvovaginitis in infants and children represents a definite therapeutic advance, since the results are in general more satisfactory than those obtained with the local instillation of antiseptic solutions or the injections of vaccine The reservation must be made however that the generally unsuccessful results with vaccines may be due to inadequate dosage

## APPLE DIET IN DIARRHEA

The apple diet in the treatment of diarrhea in infants and children merits mention because of its established value, its simplicity and its interesting historical background. Its use had a humble origin, analogous to that of smallpox vaccine, for German housewives had recognized its value long before Heister, in 1928, and Moro, in 1929, called attention to its efficacy.

Moro relates that in a prison camp during the World War epidemics of dysentery were common amongst the half starved prisoners, but that a number of them, surreptitiously ingesting forbidden fruit from several apple trees showed striking improvement in their symptoms. The camp physician used apples thereafter and reported marked success.

During the past five years favorable reports have appeared in the American literature and modifications have been introduced in an attempt to enhance the efficacy of raw apple. Apple powder, pectin-agar, cellulose, banana powder and honey have been suggested but their advantages are not yet established.

The physiological basis for the beneficial action of apple pulp in the gastrointestinal tract is not yet understood but the evidence suggests that the colloid pectin adsorbs and removes toxic substances. Organic acids, particularly malic, may supplement this colloid action by a sedative and astringent action which reduces peristalsis.

We have employed the raw apple diet in a small number of patients at the New York Hospital with promising results. The pulp of ripe apple, without the core or skin, was fed in varying amounts depending upon the infant's willingness to ingest it. An effort was made to give at least two to four tablespoonfuls every two hours for two days, supplemented by water or weak tea. On this régime, the stools assumed the character of practically pure apple within twelve to twenty-four hours and usually remained formed after boiled skimmed or protein milk was substituted in small amounts for the water at the end of forty-eight hours.

Encouraging results were obtained in both bacillary dysentery and other forms of diarrhea in older infants and children. Frequent refusal in infants under five to six months and an irritative stomatitis in infants under two months made the apple diet less practicable in this age group, but this form of treatment can be of great service to the pediatrician because its simplicity may obviate hospitalization.

In closing, I should like to point out that present progress in the study of viruses, of the biochemistry of vitamins, and of endocrinology, and in the psychiatric rapprochement with pediatrics, are harbingers of the clinical progress which may be expected in the next decades. These fundamental contributions should lead us to aspire to even higher standards for mental, emotional and physical growth and development of children.

## RECENT ACCESSIONS TO THE LIBRARY

Possession does not imply approval

- Adams, N K *The physics and chemistry of surfaces* 2 ed  
Oxford, Clarendon Press, 1938, 402 p
- Adler, A *Guiding human misfits*  
N Y, Macmillan, 1938, 88 p
- Anniversary volume, scientific contributions in honor of Joseph Hervey Pratt*  
[Lancaster Pa], Lancaster Press, 1937, 983 p
- Balveat, R M *Allergic diseases, their diagnosis and treatment* 5 ed  
Phil, Davis, 1938, 547 p
- Barsky, A J *Plastic surgery*  
Phil, Saunders, 1938, 355 p
- Beck, R C *Laboratory manual of hematology technique*  
Phil, Saunders, 1938, 389 p
- Benedict, F G *Vital energetics, a study in comparative basal metabolism*  
Wash, Carnegie Institution, 1938, 215 p
- Benedict, F G & Lee, R C *Hibernation and marmot physiology*  
Wash, Carnegie Institution, 1938, 239 p
- Berghoff, E *Religion und Heilkunde im Wandel der Zeiten*  
Wien, "Ars Medici", 1937, 171 p
- Bieling, R *Viruskrankheiten des Menschen*  
Leipzig, Barth, 1938, 114 p
- Bovd, W *Surgical pathology* 4 ed  
Phil, Saunders, 1938, 886 p
- Braeuning, H *Der Beginn der Lungentuberkulose beim Erwachsenen*  
Leipzig, Thieme, 1938, 222 p
- Buchner, O *Systematische Arbeits- und Beschäftigungstherapie für Gesunde, Nerven- und Geisteskranke*  
Wien, Gerold, 1937, 247 p
- Burke, R M *A historical chronology of tuberculosis*  
Springfield, Ill, Thomas, [1938], 84 p
- Cabot, R C & Adams, F D *Physical diagnosis* 12 ed  
Balt, Wood, 1938, 846 p
- Cattell, R B *Crooked personalities in childhood and after*  
N Y, Appleton-Century, 1938, 215 p
- Chemistry (The) of the amino acids and proteins* edited by C L A Schmidt  
Springfield, Ill, Thomas, [1938], 1031 p
- Clarke, C D *Molding and casting*  
Balt, Lucas, [1938], 308 p
- Cushing, H W *Tumeurs intracranienes*  
Paris, Masson, 1937, 194 p
- DeLee, J B *The principles and practice of obstetrics* 7 ed  
Phil, Saunders, 1938, 1211 p
- Desplas, B, Moulouquet-Doleris, P & Valgrais, P *L'exploration radiologique post-operative de la voie biliaire principale*  
Paris, Masson, 1938, 120 p
- Destot, E *Traumatismes du pied et rayons X* 2 ed  
Paris, Masson, 1937, 292 p
- Dufflo, G *La responsabilité civile des medecins*  
Paris, Maloine, 1937, 189 p
- Duhem, P *Precis de physiotherapie clinique*  
Paris, Gauthier-Villars, 1937, 603 p
- Dumesnil, R *L'ame de medecin*  
Paris, Plon, 1938, 242 p
- Effler, L R *My scrapbook of medicine*  
[Toledo, O, privately pub, 1937], 248 p
- Fisher, C, Ingram, W R & Ransom, S W *Diabetes insipidus and the neuro-hormonal control of water balance*  
Ann Arbor, Edwards, 1938, 212 p
- Frisch, F *Die Epilepsie Biologie, Klinik, Therapie*  
Wien, Weidmann, 1937, 144 p
- Fulop-Miller, R *Triumph over pain*  
Indianapolis, Bobbs-Merrill, [1938], 438 p
- Goldhahn, R *Die Operation in der Sprechstunde*  
Leipzig, Thieme, 1938, 181 p
- Hansen, H F *Reference handbook for nurses*  
Phil, Saunders, 1938, 347 p
- Harrow, B *Biochemistry for medical, dental and college students*  
Phil, Saunders, 1938, 383 p

- Hegner, R W *Big fleas have little fleas*  
Balt, Williams, 1938, 285 p
- Joussan, A J B H *Psychologie des masses*  
[Paris], Flammarion, [1937], 212 p
- Jullienne, L A *The etiology of trachoma*  
N Y, Commonwealth Fund, 1938, 248 p
- Karsner, H T *Human pathology* 5 ed  
Phil, Lippincott, [1938], 1013 p
- Kimber, D C, Gray, C E & Strickpole, C E  
*Textbook of anatomy and physiology*  
[for nurses] 10 ed  
N Y, Macmillan, 1938, 643 p
- Ludlow, (Sir) P P *Virus diseases and viruses*  
Cambridge [Eng], Univ Press, 1938,  
51 p
- Merkins, J C *The practice of medicine*  
2 ed  
St Louis, Mosby, 1938, 1413 p
- Meller, J *Augenärztliche Eingriffe* 4 Aufl  
Wien, Springer, 1938, 428 p
- Monrad-Krohn, G H *The clinical examination of the nervous system* 7 ed  
N Y, Hoeber, 1938, 319 p
- Norris, G W & Landis, H R M *Diseases of the chest* 6 ed  
Phil, Saunders 1938, 1019 p
- Osler, (Sir) W *The principles and practice of medicine*, 13 ed  
N Y, Appleton-Century, [1938], 1424 p
- Passler, H W G A *Megacolon und Megacystis*  
Leipzig, Barth, 1938, 172 p
- Reimann, H A *The pneumonias*  
Phil, Saunders, 1938, 381 p
- Rivoire, R *Les acquisitions nouvelles de l'endocrinologie* 3 ed  
Paris, Masson, 1937, 264 p
- Seyringhaus, E L *Endocrine therapy in general practice*  
Chic, Year Book Publishers, [1938],  
192 p
- Sheehan, J E *A manual of reparative plastic surgery*  
N Y, Hoeber, [1938], 311 p
- Stephani, J *Scintologie radiographique pulmonaire* 2 ed  
Paris, Doin, 1938, 129 p
- Tilney, F & Riley, H A *The form and functions of the central nervous system* 3 ed  
N Y, Hoeber, 1938, 851 p
- Vau, V & Recamier, J A M *Bec-de-lièvre, formes cliniques, chirurgie*  
Paris, Masson, 1938, 326 p
- Wilker, A E *The primate thalamus*  
Chic, Univ of Chic Press, [1938], 321 p
- Weicksel, J *Kompendium der sozialen Versicherungsmedizin*  
Leipzig, Thieme, 1938, 184 p
- Wieser, R *Der Rhythmus in der Verbrecherhandschrift*  
Leipzig, Barth, 1938, 226 p

## PROCEEDINGS OF ACADEMY MEETINGS

### STATED MEETINGS

OCTOBER 6—*The New York Academy of Medicine* Executive Session—Reading of the minutes ¶ Papers of the evening, Symposium on evaluation of sulfanilamide therapy—a] Fundamental problems of chemistry and pharmacology—mechanism of the action, E K Marshall, Jr, (by invitation), Professor of Phar-

macology and Experimental Therapeutics, Johns Hopkins University School of Medicine, Baltimore, b] Clinical aspects, Reuben Ottenberg, Assistant Clinical Professor of Medicine, College of Physicians and Surgeons, Columbia University, Discussion by Emanuel Appelbaum, Homer F Swift, William E Studdiford, Francis G Blake ¶ Report on election of members

OCTOBER 20—*The Harvey Society* (in affiliation with *The New York Academy of Medicine*) The first Harvey Lecture, Some Aspects of the Intermediary Metabolism of the Steroid Hormones, Guy F. Marrian, Professor of Biochemistry, The University of Toronto

### SECTION MEETINGS

OCTOBER 4—*Dermatology and Syphilology* Presentation of cases, Miscellaneous from—a) Clinics, b) Hospitals, c) Members ¶ General discussion ¶ Executive session

OCTOBER 7—*Surgery* Reading of the Minutes ¶ Presentation of cases—1) 1 Advanced recurrent carcinoma of the lip treated by radical excision and plastic repair, 2 Advanced recurrent basal cell carcinoma of the nose treated by radical excision and plastic reconstruction by three pedicled flaps from cheeks and forehead, William J. Hoffman, Discussion by Herbert Willy Meyer, b) Two cases of perforated marginal ulcer (gastro-jejunal), James E. Thompson, Discussion by Condict W. Cutler, Jr., c) Fibro-sarcoma of forearm with amputation, Louis Rene Kaufman Discussion by Morris K. Smith ¶ Papers of the evening—a) Cervical nodes in intracranial carcinoma, an objective method of determining operability, James J. Duffy, Discussion by William F. MacFee, b) Interscapulo-thoracic amputation for malignant tumors of the upper extremity, Bradley L. Coley, George I. Pack, Gordon McNeer (by invitation), Discussion by Norman L. Higinbotham

OCTOBER 11—*Neurology and Psychiatry* Reading of the minutes ¶ Papers of the evening—a) Transitory neurologic changes during hyperthermia, Ralph T. Collins (by invitation), Discussion by Israel Wechsler, William Snow, Richard Brickner, b) "Crichevia" nervosa—a psychoneurotic Simmond's syndrome, Irving H. Pardee, Discussion by Clarence P. Oberndorf, Robert Loeb, c) The problem of marijuana in psychiatry,

Walter Blomberg (by invitation), Discussion by Hon. Frederick L. Hakenburg (by invitation), Alexander Gettler (by invitation), Eugen Kahn (by invitation)

OCTOBER 13—*Pediatrics* Reading of the minutes ¶ Papers of the evening—Symposium on x-ray diagnosis of bone lesions in infancy and childhood Presented by the Department of Radiology of the New York Hospital, John R. Carty, Director

OCTOBER 17—*Ophthalmology* The regular meeting was postponed

OCTOBER 18—*Medicine* Reading of the minutes ¶ Papers of the evening—1) Unusual clinical types of coronary artery disease, William D. Stroud, Philadelphia (by invitation), Discussion by Lewis A. Conner, b) Changes in the form of the electrocardiogram caused by induced anoxemia. A clinical test for coronary insufficiency, Robert L. Levin, Discussion by Harold J. Stewart, c) Drug therapy in coronary artery disease, Harry Gold, Discussion by Cuthbert Eggleston

OCTOBER 18—*Dermatology and Syphilology* Presentation of Cases—Miscellaneous from—a) Clinics, b) Hospitals, c) Members ¶ General discussion

OCTOBER 21—*Orthopedic Surgery* Reading of the minutes ¶ Presentation of cases—Xanthoma of the knee, Donald E. McKenna ¶ Papers of the evening—a) Management of pathological fractures, Edgar A. Bick, Discussion by Philip Wilson and Samuel Kleinberg, b) Planning in orthopedic surgery, Maurice M. Pomerantz, Henry K. Taylor ¶ General discussion

### AFFILIATED SOCIETIES

OCTOBER 17—*The New York Roentgen Society* Presentation of cases was omitted ¶ Papers of the evening—a) The experimental and pathological aspect of leukemia, lymphosarcoma and Hodgkin's

disease, Maurice N Richter (by invitation), b] Indication for surgery, A P Stout (by invitation), c] Roentgenotherapy in leukemia, Albert Kern, Nathan Rosenthal (by invitation), d]

Roentgenotherapy of lymphosarcoma and Hodgkin's disease, Maurice Lenz  
 § Discussion opened by Lloyd F Craver (by invitation), Kenneth R McAlpin (by invitation), Ross Golden

## FRIDAY AFTERNOON LECTURES

TO BE HELD AT 4 30 O'CLOCK

1938 - 1939

December 2

*The influence of emotional factors upon physiological and pathological processes*

FRANK FREMONT-SMITH

December 9

*"Sciatic pain, its differential diagnosis and treatment*

ALAN DEFOREST SMITH

December 16

*The management of the emergencies in patients with heart disease*

CLARENCE E. DE LA CHAËLLE

January 6

*Diagnosis and treatment of some diseases of the newborn infant*

HOWARD REID CRAIG

January 13

*Functional digestive disturbances*

WALTER C ALVAREZ, Minnesota

January 20

*Bullkley Lecture Recent additions to our knowledge of the treatment of breast cancer*

FRANK E ADAIR

January 27

*The toxemias of pregnancy*

ARTHUR M FISHBERG

February 3

*Laboratory aids and their clinical value*

WILLIAM S TILLET

February 10

*The use of newer preparations of insulin in the treatment of diabetes*

WALTER R CAMPBELL, Toronto

February 17

*The newer methods of treatment of schizophrenia*

KARL M BOWMAN

February 24

*Present day treatment of non-tuberculous urinary infections*

MEREDITH F CAMPBELL

March 3

*Migraine headache—its mechanism and treatment*

HAROLD G WOLFF

March 10

*The problems presented by infections of the nasal accessory sinuses, and their management*

SAMUEL J KOPETZKY

March 24

*The recognition of obscure fevers*

GEORGE BLUMER, New Haven

March 31

*The management of obesity*

FRANK G PETTINGIL

April 7

*The endocrinological basis for gynecological organotherapy*

EMIL NOVAK, Baltimore

April 14

*Hemorrhagic states—recent clinical and therapeutic developments*

PAUL REZNIKOFF

April 21

*Chronic non-tuberculous pulmonary infections*

LOUIS HAMMAN, Baltimore

April 28

*Status hypoplasticus its bearing on all fields of medicine and a discussion of the automatic compensatory mechanisms involved*

WALTER TIMME

## PROGRAM OF STATED MEETINGS

1938 - 1939

December 1, 1938

*Serum therapy in pneumonia*

- 1 Present status of serum therapy, Russell I. Cecil
  - 2 Results with rabbit serum, Colin M. MacLeod
  - 3 Program for meeting the pneumonia situation, Wheeler D. Sutcliffe
- Discussion: Edward Tolstoi  
Jesse G. M. Bullowa  
Ralph S. Muckenfuss

January 5, 1939 — ANNUAL MEETING

*Chronic gastritis*

- 1 Recent advances in diagnosis by gastroscopy, Rudolf Schindler
- 2 Clinical aspects, Burrill B. Crohn

February 2, 1939

*Vitamins with special reference to therapy*

- 1 Vitamin A, Arthur M. Ludkin, New Haven
  - 2 Vitamin B, Norman Jolliffe
  - 3 Vitamin C, Gilbert Dilldorf, Vallhalla
- Discussion: Arthur J. Piteck, Jr.  
Soma Weiss, Boston  
Philip Finkle

March 2, 1939

*Symposium on arthritis*

- 1 Gout, Philip S. Hench, Rochester, Minnesota
  - 2 The nature of hypertrophic arthritis (degenerative joint disease), Walter Bauer, Boston
  - 3 Evaluation of newer methods of therapy, Ralph Boots
- Discussion: Philip D. Wilson  
Edward F. Hartung  
Albert B. Ferguson

May 4, 1939

*Recent advances in the treatment of peripheral vascular disease*

- 1 Clinical manifestations, Irving S. Wright
  - 2 Medical treatment, Edgar V. Allen, Rochester, Minnesota
  - 3 Surgical treatment, Reginald H. Smithwick, Boston
- Discussion: Beverly Chew Smith  
James C. White, Boston

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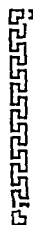
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of the body as a whole, there are processes of derivation of energy from carbohydrate which are carried on alike in each cell of all tissues. These are necessary for its own survival and vital activity. Thiamin, therefore, appears to be a fundamentally essential tool of metabolism, necessary for all living things.

What appears to be true for thiamin in high degree appears also to be true to a considerable degree for the other water soluble vitamins. Thiamin is merely the most conspicuous example, because nature's total supply is not much in excess of minimum needs and because the lack of no other accessory substance leads to so prompt, so profound and so universal a disaster.

It is consistent with this view that all plant and animal tissues contain this substance. However, the capacity for synthesis of the substance in nature is sufficiently limited so that no natural tissue is by accident super-rich in it. Whereas the majority of plant and animal tissues which are used as foods contain about one-half part per million of it, the richer foods contain only three to five parts per million. Notable among these are the seeds which constitute a principal repository of the substance in the plant world. The germs and bran coats of grains may contain thirty to fifty parts per million, these larger amounts being stored in the seed to care for the growth of the plant until it puts forth leaves to the sun and can then resume synthesis of the vitamin. Many of the lower plants have very meager capacity for its synthesis, some lack it entirely, none produce a plethora of it. The richness of brewers' yeast in vitamin content is primarily due to seizure of it from the grain wort in which the yeast is grown. If nature as a whole operates on an economy of scarcity with respect to this substance, it is not surprising that mankind should appear to do so also.

The foods may be divided into three groups:

- A Thiamin-rich foods, notably seeds, lean pork, and to a lesser extent milk and the internal organs of mammals
- B Thiamin-poor foods, such as highly milled grains, hominy, macaroni, polished rice, white bread, sugar
- C Indifferent foods which comprise everything else except fats. These foods, such as fruits and vegetables, contain significant amounts of thiamin per unit of dry weight but do not provide a sufficient surplus to make up for the deficiencies of the thiamin-poor foods, unless the latter are used in relatively small quantities.

D The Fats These do not require thiamin for their metabolism and in so far as they serve to displace foods of class B from the dietary, they have a very valuable protective effect

We recently have had occasion to reanalyze seventy diets associated with historical outbreaks of beriberi and about thirty diets associated with absence or recession of the disease. The diets in question are among those previously analyzed by Cowgill. After trying various indices, we found that the ratio between the thiamin content of the food and its non-fat calorie content is an excellent index of the appearance or non-appearance of beriberi. If the thiamin is stated in micrograms (millionths of a gram) and the calorific content in small calories, we get a relationship

$$\frac{\text{thiamin}}{\text{non-fat calories}} = 3$$
 as representing the borderline between beriberi and non-beriberi

This index also fits quite well the diets of the working classes in the United States, to judge from a considerable number of them to which it has been experimentally applied. The contrast between the Oriental beriberi-producing diets and poor class American diets is not great with respect to thiamin content. The latter diets owe such superiority as they possess as much to the presence of larger amounts of fat as they do to the presence of larger amounts of thiamin. American diets in which white bread, corn meal and like products make up a large part of the calories are near the beriberi borderline. The diets of more prosperous people show a considerably larger margin of safety due principally to the lesser proportions of starchy foods. It should be said, however, that many of the Oriental diets used by peoples who are not addicted to the milling of grain often contain as much or more thiamin than the average American diet.

An attempt has been made by Cowgill to relate the thiamin requirement to the individual weight. He concluded on the basis of animal experiments that the thiamin requirement of an individual is proportional to weight<sup>5/3</sup>, that is, that in a series of individuals the requirement rises much more rapidly than the weight. The experiments in question were performed before it was well recognized that there is a large number of B vitamins. In the light of recent knowledge, the basal diets which were used were deficient with respect to several of these factors. We believe that the apparent rising proportional require-